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OBSTETRICS AND GYNECOLOGY

TRANSACTIONS OF THE TWENTY-SEVENTH ANNUAL MEETING OF THE PACIFIC COAST OBSTETRICAL AND GYNECOLOGICAL SOCIETY

Editor in Chief
HOWARD C. TAYLOR, JR.

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Transactions of the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society

In the pursuit of excellence. President's address George E. Judd, M.D., Los Angeles, California	1073
Public relations in our maternity wards Purvis L. Martin, M.D., and Steward H. Smith, M.D., San Diego, California	1079
Spontaneous premature rupture of the membranes Melvin W. Breese, M.D., Portland, Oregon	1086
Usefulness of paracervical block in obstetrics Emery P. Page, M.D., Michael L. Kamm, M.D., and Clifford G. Chappell, M.D., Berkeley, California	1094
Symposium on endometrial cancer	
Introduction James F. Nolan, M.D., Los Angeles, California	1099
Incidence Arthur B. Nash, Victoria, British Columbia	1100
Problems in diagnosis of cancer of the endometrium Herbert F. Traut, M.D., San Francisco, California	1102
Histology in relation to carcinogenesis Richard L. Taw, Los Angeles, California	1103
Treatment Charles E. McLennan, M.D., Palo Alto, California	1104
Continuing evaluation Axel N. Arneson, M.D., St. Louis, Missouri	1106

(Contents continued on page 2)

Contents continued from page 1

The clinical value of peritoneal lavage for cytologic examination Daniel G. Morton, M.D., J. George Moore, M.D., and Norman Chang, M.D., Los Angeles, California		1115
Genital tuberculosis in women Karl L. Schaupp, Jr., M.D., San Francisco, California		1126
Studies of the isolated perfused human placenta. I. Methods and organ responses R. Jonathan Goerke, M.D., Charles M. McKean, M.D., Alan J. Margolis, M.D., Mary Beth Glendening, Ph.D., and Ernest W. Page, M.D., San Francisco, California		1132
Studies of the isolated perfused human placenta. II. Progesterone content of perfusates C. A. Woolever, M.D., Alan Goldfien, M.D., and Ernest W. Page, M.D., San Francisco, California		1137
Serum lipids in pre-eclampsia-eclampsia Russell R. de Alvarez, M.D., and Gloria E. Bratvold, B.S., Seattle, Washington		1140
Pregnanediol excretion in threatened abortion Charles F. Langmade, M.D., Solomon Notrica, Ph.D., James Demetriou, Ph.D., and Arnold G. Ware, Ph.D., Los Angeles, California	(1149
Unusual lesions of the reproductive tract in infants and children James V. McNulty, M.D., and Newlin Hastings, M.D., Los Angeles, California		1157
Enterocele Gerald E. Kinzel, M.D., Portland, Oregon		1166
Management of early carcinoma J. George Moore, M.D., Daniel G. Morton, M.D., John W. Applegate, M.D., and William Hindle, M.D., Los Angeles, California		1175

(Contents continued on page 4)

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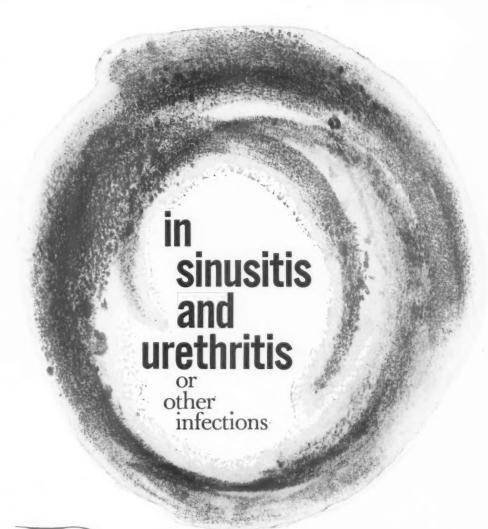
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Obstetrics

The incompetent cervix	Physiologic or dysfunctional incompetence of the cervix Robert G. Hunter, M.D., George W. Henry, M.D., and Charles S. Judd, Jr., M.D., Honolulu, Hawaii	1183
	Review of 36 Shirodkar operations Joseph R. Brandy, M.D., and John H. Peterson, M.D., Buffalo, New York	1191
	Simple treatment of the incompetent cervical os Meyer Vitsky, M.D., Richmond, Virginia	1194
Ectopic pregnancy	Atypical changes of genital epithelium associated with ectopic pregnancy Herbert W. Birch, M.D., and Conrad G. Collins, M.D., New Orleans, Louisiana	1198
	Cellular atypia in endometrial glands (Arias-Stella reaction) as an aid in the diagnosis of ectopic pregnancy Abraham Mackles, M.D., Samuel A. Wolfe, M.D., and Samuel N. Pozner, M.D., Brooklyn, New York	1209
	The suspected ectopic pregnancy Robert E. Hall, M.D., and W. Duane Todd, M.D., New York, New York	1220
	Unilateral twin tubal pregnancy M. Leo Bobrow, M.D., and Irving Schreiber, M.D., New York, New York	1230
Complications of pregnancy	Antenatal pulmonary embolic disease M. Alex Krembs, M.D., and Thomas J. Kozina, M.D., Milwaukee, Wisconsin	1233
	Antepartum pulmonary embolism Michael Klein, M.D., Morris H. Sable, M.D., and Richard M. Zirkin, M.D., Cleveland, Ohio	1237
	Severe hypokalemia due to prolonged administration of chlorothiazide during pregnancy Jack A. Pritchard, M.D., and P. J. Walley, M.D., Dallas, Texas	1241
	Trial of thalidomide in insomnia associated with the third trimester R. O. Nulsen, M.D., Cincinnati, Ohio	1245

(Contents continued on page 6)



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Contents continued from page 4

Lidocaine or dibucaine for saddle block anesthesia—an analysis William F. Peterson, Lt. Colonel, USAF (MC),	1249
Washington, D. C.	
Maternal and fetal effects of obstetric analgesia C. Ray Potts, M.D., and John C. Ullery, M.D., Columbus, Ohio	1253
The effect of analgesia and anesthesia on the initial fetal respirations Clifford R. Taylor, M.D., Buffalo, New York	1260
Department of current opinion	
Management of eclampsia	1266
Editorials	
Editoriais	
The Pacific Coast Obstetrical and Gynecological Society	1276
The research training grants program in developmental biology, 1961	1276
Correspondence	
Correspondence	1280
Reviews and abstracts	
Reviews of new books	1281
Books received for review	1286
Selected abstracts	1286
Indov	
Index	
Author index	1291
	anesthesia—an analysis William F. Peterson, Lt. Colonel, USAF (MC), Washington, D. C. Maternal and fetal effects of obstetric analgesia C. Ray Potts, M.D., and John C. Ullery, M.D., Columbus, Ohio The effect of analgesia and anesthesia on the initial fetal respirations Clifford R. Taylor, M.D., Buffalo, New York Department of current opinion Management of eclampsia Editorials The Pacific Coast Obstetrical and Gynecological Society The research training grants program in developmental biology, 1961 Correspondence Correspondence Reviews and abstracts Reviews of new books Books received for review Selected abstracts

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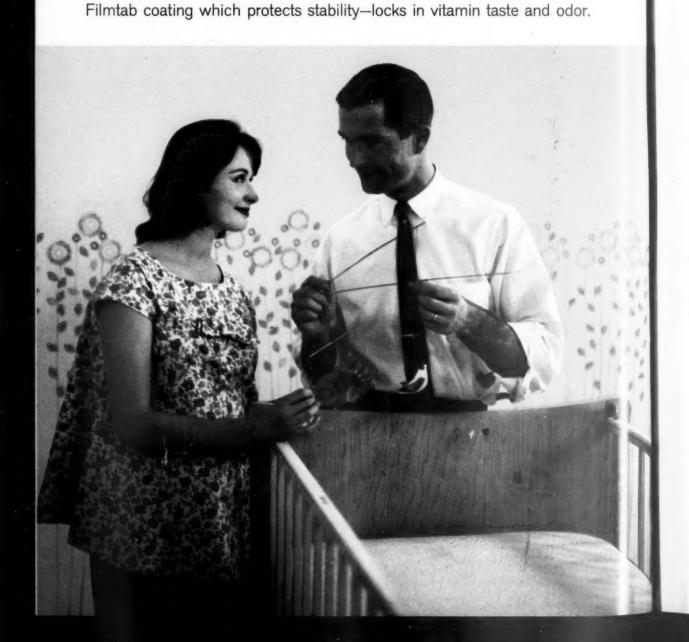
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total	329	264	52	13

When there is inflammation, swelling and pain from obstetrical or gynecologic conditions or procedures, Chymoral suppresses inflammatory reaction, dissipates edema and blood extravasates in the tissues, restores regional small blood vessel flow and advances the healing process.

1. Teitel, L. H., et al.: Indust. Med. 29:150, 1960. 2. Clinical reports to the Medical Dept., Armour Pharmaceutical Company, 1959. 3. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Amer. Med. Assoc. Conv., Miami, Fla., June, 1960.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS • Armour Means Protection

CHYMORAL

controlled inflammation, curtailed swelling, curbed pain ...produced excellent or good results in 8 out of every 10 cases¹⁻⁴

CHYMORAL

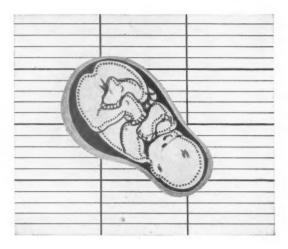
Chymoral is an ORAL anti-inflammatory enzyme tablet specifically formulated for intestinal absorption. Each tablet provides enzymatic activity, equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravastes; helps to liquefy thick tenacious mucous secretions; improves regional circulation; promotes healing; reduces pain. NIDICATIONS: Chymoral is indicated in respiratory conditions such as asthma, bronchitis, rhinitis, sinusitis; in accidental trauma to speed absorption of hematoma, bruises, and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions such as pelvic inflammatory disease and mastitis; in obstetrics as episiotomies and breast engorgement; in surgical procedure as biposies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disease as biposies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disease; provides as episiotomies as well as denerally accepted measures may be coadministered. SIDE EFFECTS: Mild gastric upsets, rarely encountered. DOSAGE: Recommended initial dose is two tablets q.l.d.; one tablet q.l.d. for maintenance. SUPPLIED: Bottles of 48 tablets.

ORAL systemic antiinflammatory enzyme tablet now in threatened premature delivery

Dactil-OB

Brand of piperidolate hydrochloride, hesperidin complex and vitamin C

maintains gestation / increases fetal survival rate

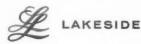


"Dactil has been used as a preventive measure with great success and with no untoward effects."

In a study of 618 pregnancies over a period of 4 years, premature births were reduced from 13.1% of 168 patients without Dactil to 4.7% of 450 patients with Dactil.² In the treated patients birth weights were increased.

Dosage: 1 tablet q.i.d. from the beginning of pregnancy in any patient with a history of previous difficulty. For more information send for Dactil-OB brochure.

(1) Stephens, L. J.: Prevention of Premature Delivery: Am. J. Obst. & Gynec. 70:6 (June) 1958. (2) Stephens, L. J., in press.



nec

GREATER PATIENT COMFORT and safety with DYCLONE

the unsurpassed topical anesthetic

for instrumentations examinations pain pruritus

DYCLONE does more...safely...than any other topical anesthetic because it is

fast-acting long-acting antibacterial antifungal nonsensitizing

supply...Dyclone Creme, tubes of 1 oz. with rectal applicator. Dyclone Solution, bottles of 1 and 8 oz.





PITMAN-MOORE COMPANY
DIVISION OF THE DOW CHEMICAL COMPANY
INDIANAPOLIS 6, INDIANA

for pre- and postnatal lower urinary tract infections consider the safety and efficacy of

MANDELAMINE

the urine-specific antibacterial

Mandelamine's demonstrated safety makes it the ideal drug to eliminate lower urinary tract infections complicating pregnancy or the puerperium. By its antibacterial action in the urine, Mandelamine also helps prevent ascending pyelonephritis.

Urine-specific Mandelamine destroys most urinary pathogens (including many strains resistant to antibiotics and sulfonamides) without producing resistant mutants. Sensitization and superinfections do not occur after prolonged use, and Mandelamine is economical therapy.

Dosage: Adults—Two Mandelamine Hafgrams four times a day. Precautions: Mandelamine is contraindicated in patients with renal insufficiency and/or severe hepatitis. An occasional patient may experience gastrointestinal disturbance. Supplied: Mandelamine Hafgram® tablets (0.5 Gm.), and pleasantly flavored Mandelamine Suspension.



Full dosage information, available on request, should be consulted before initiating therapy.

TEDRAL GELUSIL PROLOID PERITRATE

MORRIS PLAINS, N.J

QP1





to relieve the symptoms of premenstrual tension

for EDEMA... CYCLEX provides the prompt diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES...CYCLEX supplies the effective relief of meprobamate for nervousness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS...CYCLEX affords quickacting relief of nausea and bloating associated with premenstrual tension

SUPPLIED: Tablets, bottles of 100. Each tablet contains 25 mg of HYDRODIURIL (hydrochlorothiazide) and 200 mg. of meprobamate.

DOSAGE: Usual adult dosage is one tablet once or twice a day, beginning on the first morning of symptoms and continuing until the onset of menses. CYCLEX may be continued through the menstrual period.

Before prescribing or administering CYCLEX, the physician should consult detailed information on use accompanying package or available on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., INC.



MERCK SHARP & DOHME Division of Merck & Co., INC. West Point, Pa.



NOW A

POSITIVE*

SEPARATION OF THE FETAL AND MATERNAL

EG

FETAL HEART

PROVIDES CONSTANT ELECTRONIC MONITORING OF FETUS DURING LABOR AND DELIVERY

Through electronics, the Fetal Heart Monitor provides a complete isolation of the fetal heart rate from the maternal rate... during labor and delivery. An electrode of spring steel attaches to the fetus' scalp with the electronic circuit completed with two standard, plate-type electrodes. The electrode may be left attached for hours with no difficulty or distress to the fetus or mother.

INSTANT RECOGNITION OF FETAL DISTRESS

During labor and delivery the obstetrician receives a positive signal from the fetus both during and between contractions. This constant, accurate fetal rate can be observed on the heart rate meter and oscilloscope and may be heard through speakers. A permanent record of rate tracing can be made by attaching to any standard electrocardiograph.



ELECTRODE EASILY PLACED

Surgically sharp points are brought together on a fold of fetal scalp by moving a sliding sleeve. Electrode is detachable for sterilization in an autoclave.

Write for brochure or additional information.





A Technic for Recording Fetal ECG During Labor and Delivery by Chas. A. Hunter, Jr., M. D., et al. 16:567, 1960. Obst. and Gynec.

- 1

MEPROBAMAT

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ould consult on request.

6 ANSWERS TO THE QUESTION:

What's New in Gynecology and Obstetrics?

OBSTETRICAL ENDOCRINOLOGY by José Botella Llusia, Univ. of Madrid, Spain. A short, practical introduction to the main problems of the endocrinology of pregnancy, labor, and puerperium. Each chapter includes detailed references to the latest literature for further study of the problems under discussion. Copiously illustrated. Pub. date June '61 (Amer. Lec. Gynecology and Obstetrics)

PREMATURITY: The Diagnosis, Care and Disorders of the Premature Infant by Beryl Corner, United Bristol Hospitals. The philosophy of the author, who is a clinician and teacher of wide experience in this sphere, is to stress the need for critical evaluation based on an understanding of "the natural tenderness and weakness" of these infants. Hence the important inclusion of a detailed section on the anatomy and physiology of prematurity—unique in this type of book. Includes an extensive bibliography, many original drawings and photographs. Pub. date Sept. '60, 602 pp., 242 il., \$21.00

CARCINOMA IN SITU OF THE UTER-INE CERVIX: A Study of 235 Cases from the Free Hospital for Women by Gilbert H. Friedell, Arthur T. Hertig, and Paul A. Younge, all of Harvard Medical School. A detailed study for those concerned with the diagnosis and management of carcinoma in situ of the uterine cervix. Even in the section devoted to pathologic with clinical findings. Describes methods for handling biopsy, conization, and hysterectomy specimens in the laboratory for best evaluation of extent of the disease. Pub. date Aug. '60, 164 pp., 98 il. (6 full color plates), \$7.50

TWINS IN HISTORY AND SCIENCE by Luigi Gedda, Instituto Di Genetica Medica, Rome. Although much has been written on the subject of twins, this is the first complete and comprehensive study. Gedda has made use of all available data, including his own personal observations. This book will be of interest to everyone concerned with biological and biopathological problems. It is well-written and excellently illustrated. Pub. date July '61, 292 pp. (7½ x 10), 294 il.

FETAL ELECTROCARDIOGRAPHY: The Electrical Activity of the Fetal Heart by S. D. Larks, Univ. Calif. This pioneering monograph makes available and understand-

able the powerful new technique of fetal electrocardiography. Covers the fetal ECG from the time of its earliest appearance right through the months of gestation to delivery. Potentialities for drug investigations as well as for studies of maternal-fetal relationships are presented. Provides a new dimension in cardiac understanding. Pub. date Dec. '60, 128 (63/4 x 93/4) pp., 70 il. (Amer. Lec. Gynecology and Obstetrics edited by E. C. Hamblen), \$6.50

GYNECOLOGICAL UROLOGY (32 Contributors from eight countries). Edited by A. F. Youssef, Cairo Univ. Eminent specialists from eight countries open up, explore, and reveal in forty-two chapters a no-man's land that has, until recently, been but sparsely dealt with. Beautifully illustrated by 367 figures on anatomic principles, pathologic conditions, radiographic appearances, diagnostic procedures, apparatus, and surgical techniques. Pub. date July '60, 916 pp., 367 il., \$22.50

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CHARLES C THOMAS • PUBLISHER
301-327 East Lawrence Avenue
Springfield • Illinois

in postmenopausal vaginitis in vaginal plastic surgery

ORTHO®

Dienestrol CREAM

vaginal estrogen therapy

builds vaginal epithelium





effective therapy in the critical pH zone



Massengill[®] Powder

The buffered acid vaginal douche with low surface tension

The normal pH of the vagina (3—4.5) inhibits the growth of most pathogens, but several factors such as menstruation and vaginal infections may cause the vaginal pH to rise... thus promoting greater growth of pathogens.

A simple acid douche will restore normal vaginal pH, but it is quickly neutralized by the alkaline mucosa and pH rises again. An effective therapeutic agent must be buffered to maintain the pH for several hours and must also be able to penetrate the folds of the vaginal mucosa for effective cleansing.

FORMULA: Ammonium Alum, Boric Acid, Phenol, Eucalyptol, Berberine, Menthol, Thymol and Methyl Salicylate.



A Massengill Powder douche provides effective therapy because it:

1 RESISTS NEUTRALIZING

The buffered acid douche solution of Massengill Powder (pH 3.5-4.5) resists neutralizing. And this normal, low pH is maintained for 4 to 6 hours in ambulant patients... and as long as 24 hours in recumbent patients.

- 2 INHIBITS PROPAGATION OF PATHOGENS

 Low pH of Massengill Powder solution inhibits propagation of monilia, trichomonas vaginalis and pathogenic bacteria while simultaneously promoting growth of beneficial Döderlein bacilli.
- Denetrates vaginal mucosal folds

 Low surface tension of Massengill Powder solution is 50 dynes/cm. (vinegar is 72 dynes/cm.). This enables it to penetrate and cleanse folds of the vaginal mucosa. And this low surface tension makes cell walls of infecting organisms more susceptible to therapy.
- WON'T DEVELOP RESISTANT STRAINS

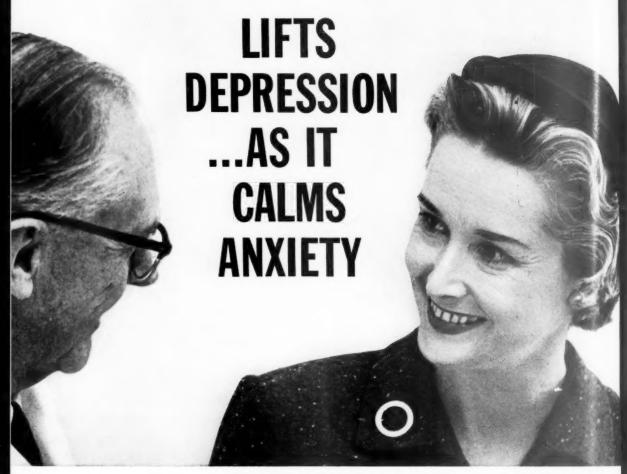
 Because normal pH is restored, normal environment is created . . . pathogens can't thrive . . . resistant strains can't develop as with antibiotics.
- 5 IS ACCEPTABLE TO PATIENTS

 Clean, refreshing fragrance of Massengill Powder is acceptable to the most fastidious. Solutions are easily prepared, convenient to use, nonstaining . . . also mildly astringent and soothing to inflamed mucosa.

Write for samples and literature

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE
KANSAS CITY • NEW YORK • SAN FRANCISCO



"I feel like my old self again!" Thanks to your balanced Deprol therapy, her depression has lifted and her mood has brightened up - while her anxiety and tension have been calmed down. She sleeps better, eats better, and normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient - they often aggravate anxiety and

And although amphetamine-barbiturate combinations may counteract excessive stimulation they often deepen depression and emotional fatigue.

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety - a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly - you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly - often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely-no danger of liver or blood damage. Deprol does not cause liver toxicity, anemia, hypotension, psychotic reactions or changes in sexual function - frequently reported with other drugs.

'Deprol'

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d. Composition: 1 mg. 2-diethylaminoethyl benzilam hydrochloride (benactyzine HCI) and 400 mg. meprobarate. Supplied: Bottles of 50 light-pink, scored table. Write literature and samples.



HE BENEFITS OF **SUSTAINED RELEASE IRON PLUS A FECAL SOFTENER**

SUSTAINED RELEASE IRON CAPSULES LEDERLE

SPECIAL NEEDS

A rational approach to the increased iron needs and increased G.I. sensitivity of pregnant patients. Sustained timed action releases iron in the area of optimal

uptake - primarily in the duodenum-jejunum, and some in the ileum. The possibility of G.I. irritation is reduced because ferrous fumarate is a better tolerated form of iron, and because the concentration of iron is never unduly high at any point. FERRO-SEQUELS also contain dioctyl sodium sulfosuccinate which helps soften stools for easier elimination.

Each two-tone, green FERRO-SEQUELS contains:

PERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



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13

longer-acting, fewer injections for fetal salvage with no androgenic effect

Squibb Hydroxyprogesterone Caproste

Long-acting Progestational Therapy

Delalutin offers these advantages over other progestational agents: Significantly improved rate of fetal salvage¹-³ ■ No virilizing effect on female fetus or mother ■ High, sustained hormonal level in the

High, sustained hormonal level in the uterine muscle and mucosa⁴ — high enough even to replace an excised corpus luteum⁵

■ Absence of local tissue reactions³.

Comparative artest of Single inflatements in the projection of Defaultin and progressions on the project of the Duration of Action of 17-Alpha-Hydroxy-progressors-n-Caprosic (Defaultin). The South Institute for Medical Research, ther 17, 1953.

Hydroxyprogesterone Caproate (Defaultin)

Progesterone

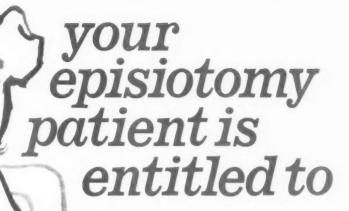
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as a project of the Duration of Action of 17-Alpha-Hydroxyprogesterone Caproate (Defaultin)

Progesterone

4

Days following injection



WARIDASE

STREPTOKINASE-STREPTODORNASE LEDERLE

for a faster recovery with more

comfort

Inflammation, swelling, and pain are reduced more rapidly when VARIDASE is added to your post-partum regimen. Your patient has a more comfortable convalescence and a faster return to normal activity.

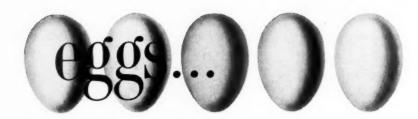
<u>Precautions:</u> VARIDASE has no adverse effect on normal blood clotting. Care should be taken in patients on anticoagulants or with a deficient coagulation mechanism. When infection is present, VARIDASE Buccal Tablets should be given in conjunction with antibiotics.

<u>Dosage</u>: One buccal tablet four times daily usually for five days. To facilitate absorption, patient should delay swallowing saliva.

Supplied: Each tablet contains 10,000 Units Streptokinase, 2,500 Units Streptodornase. Boxes of 24 and 100 Tablets.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York





and the fat recommendation

in current dietary thinking Cholesterogenesis in man is recognized as a highly complex process, only partially affected by the character of the diet. Nonetheless, the opinion is often expressed that the lipid content of the adult American diet might well be reduced from its current level of 40 to 50% of daily calories to about 30%.

The ultimate goal of this recommendation is the possible reduction of serum cholesterol levels.

Because eggs constitute an important part of protein, vitamin, and mineral nutrition, they are included in virtually every authoritative low fat diet. In a diet supplying 2500 calories, 30% of which are furnished by lipids, the lipids of two eggs comprise only 1/7 of the allowed daily fat intake.

Two Eggs Provide*:

Protein13	Gm.
Carbohydrate1	Gm.
Fats (total lipids)12	Gm.
Fatty acids	
Saturated (total)	Gm.
Unsaturated	
Oleic acid 5	Gm.
Linoleic acid	Gm.

Vitamins present: A, D, E, K, B₁, B₂, B₆, B₁₂, pantothenic acid, niacin, folic acid, biotin.

Minerals present: Calcium, phosphorus, sodium, potassium, chlorine, sulfur, iron, iodine, manganese, magnesium, zinc, copper.

*U. S. Department of Agriculture Home and Garden Bulletin No. 72, Sept. 1960.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Poultry and Egg National Board 8 South Michigan Avenue, Chicago 3, III.

in monilial vaginitis start therapy with the true specific

gentia-jel

it works when others fail



- QUICKER CURES AND LESS RECURRENCES
- . FAST RELIEF OF VULVAR ITCHING AND BURNING
- SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION

In Monilial
Vaginitis
why wait until
other therapies
fail...start your
patients with
gentia-jel

CURES ARE QUICKER . . . RECURRENCES LESS

Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrences. Gentia-jel contains gentian violet, the most effective agent known for the destruction of Monilia albicans. Its remarkable effectiveness is proved by its high rate of cures during the last trimester of pregnancy when vaginal mycotic infections are most difficult to cure.

FAST, GRATIFYING RELIEF OF VULVAR ITCHING AND BURNING. This soothing jel provides fast relief of vulvar itching and burning. This all important relief is often much faster than that provided by solid dosage forms such as tablets and suppositories.

DISPERSES AND PENETRATES INTO ALL FOLDS. Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia to destroy fungi and bacteria.

SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION. Gentia-jel's applicators, unlike many, are never reused, they are discarded...eliminating a major cause of reinfection. The disposable applicators are more esthetic to the patient... and greatly appreciated.

EASIER FOR YOUR PATIENTS TO USE. (1) At bedtime, patient lies back with knees flexed, inserts applicator and instills Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

YOUR PRESCRIPTION SHOULD BE FOR TWELVE. Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators. Contains: gentian violet 0.1%; lactic acid 3%; acetic acid 1.0%; in a water-soluble polyethylene glycol base.

gentia-jel

the true specific for monilial vaginitis

NEW—the first complete HEMATINIC at a cost comparable to straight iron therapy

STUARTINIC

in a one tablet dose

STUARTINIC provides the highest amount of elemental iron in a single tablet.

Complete

Therapeutic amounts of ferrous fumarate plus a bonus of Vitamin B Complex and Vitamin C.

More effective

More effective than ferrous gluconate or ferrous sulfate.

Better tolerated

Less irritating, less nauseating, less toxic than other iron preparations.**

Lower in cost

The lowest cost complete Hematinic for iron deficiency anemias.

One tablet dosage

One small tablet per day provides enough iron for most patients.

PASADENA, CALIFORNIA

Stuart

THE STUART COMPANY

Each STUARTINIC tablet provides: IRON (from ferrous furnarate)
COPPER SULFATE VITAMIN B COMPLEX

B₁ (thiamine mononitrate).

B₂ (riboflavin) Bo (pyridoxine hydrochloride) Niacinamide 2 mg 100 mg 50 mg d-Calcium Pantothenate Available at all pharmacies in bottles of 100 tablets Blood, 15:540 (April) 1960. Am. Pract. & DigestTreat., 10:461 (March) 1959.



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Three of these women have vaginitis (trichomonal, monilial or mixed). Only <u>comprehensive</u> therapy can reach all three.

For every 2 cases of vaginitis caused by Trichomonas vaginalis alone, there is usually 1 case caused by Candida (Monilia) albicans, Haemophilus vaginalis, or mixed infection involving several pathogens. You can reach all of these vaginitis patients with the comprehensive vaginal preparation effective against C. albicans, H. vaginalis and other bacterial pathogens, in addition to T. vaginalis.

1. Powder for weekly application in your office: Furding (furazolidone) 0.1% and Micofur® (nifuroxime) 0.5%, in an acidic water-dispersible base. 15 Gm. plastic squeeze bottle. 2. Suppositorizes for continued home use: first week 1 in the morning and 1 on retiring. After first week, 1 at night may suffice. Continue treatment during menses and throughout menstrual cycle and for several days thereafter. Contain Micofur 0.375% and Furding 0.25% in a water-miscible base. Boxes of 12 or 24 suppositories with applicator.

TRICOFURON

1. Coolidge, C. W.; Glisson, C. S., Jr., and Smith, A. A.: J. M. A. Georgia
48:167 (Apr.) 1959. 2. Ensey, J. E.: Am. J. Obst. & Gynec, 77:155 (Jan.) 1959.
3. Frech, H. C., and Lanier, L. R., Jr.: J. M. A. Georgia 47:498 (Oct.) 1958.
EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK



Dulcolax

the laxative bibliography



The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation

The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

Predictable Action

With Dulcolax tablets action is almost invariably obtained overnight...with suppositories action occurs within the hour.

Wide Application

Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

Geigy Pharmaceuticals Division of Geigy Chemical Corporation Ardsley, New York DU 568-60 (min)



Stuart WHEN ADDITIONAL SUPP Prenatal offers greater

NUTRITIONAL SUPPORT IS REQUIRED

ONE TABLET CONTAINS:

Vitamins:

A																			5,000	USP	Units
																			400		
C																			75	mg.	
B,																				mg.	
																			3	mg.	
B.																			3.3	mg.	
B,	2	(C	C	b	a	la	31	ni	in	1)								4	mcg	
	1	r	9	n	1	k	DI	16	X	-	1:	21							. 2.7	mcg	
Ni	a	C	i	1	al	m	ic	de											20	mg.	
d-	C	a	l	C	u	П	n	P	a	n	to	rt	h	èΓ	18	t	e		3.3	mg.	
K																			0.5	mg.	
*5	ta	18	r	ť	8		b	10	rp	ot	io	n-	61	th	31	ne	ii	20	compl	ex Xe	

of vitamin B₁₂ (B₁₂ from cobalamin).

Minerals:

Ferrous Fumarate	2 gr.
(provides 42 mg. elemental iron)	
Calcium Sulfate-anhydrous 11	90 mg.
(provides 350 mg. calcium)	
lodine 0.	.05 mg.

Also trace minerals as follows:

copper, 0.25 mg.; manganese, 0.33 mg.; zinc, 0.1 mg.; magnesium, 1.67 mg.; and potassium 1.67 mg.

eofactrin (B₁₂ with intrinsic factor concentrate, non-inhibitory,

Dosage: 1 tablet daily or as directedafter meals.

May be recommended or prescribed.

Bottles of 100 tablets and Economy Pack of 225 tablets. At all pharmacies.

cost

low



THE STUART COMPANY PASADENA, CALIFORNIA





ECONOMY PACK SIVES \$1.25 in this decor



in Ob-Gyn practice: prevent bacterial insult to traumatized cervicovaginal tissue

FURACIN

brand of nitrofurazone a safe, single agent with singular benefits

From a recent study reporting the lowered incidence of postoperative morbidity following the use of Furacin Vaginal Suppositories in operative gynecology—"Certainly a single agent is to be preferred to a combination of agents, providing com-

parable results are obtained."*

Used before and after cervicovaginal surgery, delivery, radiation therapy and certain office procedures, Furacin controls infection, hastens healing, reduces discharge, malodor and discomfort.

FURACIN VAGINAL SUPPOSITORIES: FURACIN 0.3% in a water-miscible base. Box of 12, each 2 Gm. suppository hermetically sealed in yellow foil.

Furacin cream: Furacin 0.2% in a water-miscible cream base. Tube of 3 oz. with plastic plunger-type applicator.

*Grimes, H. G., and Geiger, C. J.: Am. J. Obst. & Gynec. 79:441, 1960.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK



IN GERIATRIC AGIT IT

The version of the contract of

n Ge eriat vere p

Mellaril

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

> and "screens out" certain side effects of tranquilizers, making it virtually free of:

UNDICE SENSITIVITY

The value of the phenothiazines as tranquilizers has been established. [However] many disessing side effects have been reported with these drugs.... Thioridazine [Mellaril] is as ffective as the best available phenothiazine, but with appreciably less toxic effects than lose demonstrated with other phenothiazines."

Geriarics "This is the third time the authors have evaluated a tranquilizer in a eriatric group. Our feeling is that Mellaril is superior to the other two, both of which ere ph nothiazine derivatives."2

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients - 10 or 25 mg. t.i.d.; Psychotic patients

Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg.,

Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959.
 Judah, L., Murphree, O., and Seager, L.: Am. J. Psychiat. 115:1118, June 1959.



INTODUCING

GIORLUIATE (norethindrone acetate, Parke-Davis)

for ligher progestational efficacy in • amenorrhea • menstrual irregularity • dysmenorrhea functional uterine bleeding • endocrine infertility • abortion, habitual or threatened • premenstrual tension • endometriosis

chenically...17-alpha-ethinyl-19-nortestosterone acetate—the acetate ester of nore-thingrone.

physiologically...an effective progestational agent—in this respect, exceeding not only oral ethisterone and parenterally administered progesterone but norethindrone as well. Indeed, neither NORLUTATE nor its parent product Norlutin* (norethindrone, Parke-Davis) is exceeded in potency by any other oral progestational agents, as determined by clinical assay.

clinically...makes oral progesterone replacement therapy more effective in lower dosage by providing a milligram for milligram potency approximately twice that of norethindrone.* Thus, NORLUTATE offers a superior means of promptly offsetting endogenous progesterone deficiency. May also be used as a test for pregnancy.

Therapy with NORLUTATE should be adapted to the specific indication and therapeutic response of the individual patient. Suggested dosages are based on experience with both norethindrone and NORLUTATE and take account of the increased potency of the latter. See medical brochure for details of administration and dosage.

PRECAUTIONS: The parent substance, norethindrone, has been reported as associated with masculinization of the female fetus, voice changes, hirsutism, and acne; and the possibility of such effects with NORLUTATE should be considered. Mild side effects such as transient lethargy and nausara have been reported. Spotting before calculated onset may indicate insufficient dosage.

PACKAGING: 5-rng, scored tablets, bottles of 30. «Junkmann, C.: Unpublished sports cited by Werner-Boschann, H.: Ann. New York Acad. Sc, 71:727-752, 1958.

PÄRKE-DAVIS



dual control

of severely inflamed hemorrhoids, proctitis, cryptitis, anal pruritus

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DESITIN HO hemorrhoidal SUPPOSITORIES

with hydrocortisone

for rapid, dramatic relief of severe inflammation, pain, pruritus and edema; 2 daily for up to 6 days.





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to maintain patient comfort ...they soothe, protect, lubricate, aid healing.

both suppository formulas contain healing cod liver oil

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Caroid and Bile Salts Tablets correct constipation physiologically by aiding protein digestion, increasing the flow of bile into the gut, and stimulating peristalsis. R two tablets two hours after breakfast and at bedtime.

Caroid®& Bile Salts Tablets-digestant-choleretic-laxative. American Ferment Division, Breon Laboratories, Inc., New York 18, New York

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the NEW Softab*

nausea and vomiting of pregnancy

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BUC CCI

pleasant-tasting Softab*
melts quickly in the mouth—
no water needed
attacks basic causes centrally
and peripherally
contains both antiemetic
and antispasmodic
longer acting—lower in cost

Each Softab contains:

Buclizine Hydrochloride	50 mg.
Vitamin B.	10 mg.
Scopolamine (Hyoscine)	

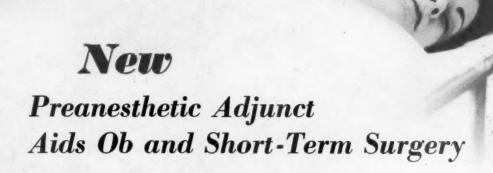
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acts for 3-4 hours cuts recovery-room time

Predictable, short-acting Largon provides sedation that relieves apprehension and produces a light sleep. It enhances the action of analgesics and anesthetics, reducing the need for CNS depressants and extending the margin of safety. Its short action, similar to meperidine, permits repeat doses without overlapping effect. Also provides antiemesis. Largon has not been observed to produce maternal or fetal depression, jaundice or blood dyscrasias, or adverse cardiovascular effects.

Supplied: LARGON, 20 mg. per cc. in Water for Injection U.S.P., available in ampuls of 1 and 2 cc., packages of 25. For further information on prescribing and administering LARGON, consult current Direction Circular enclosed with medication, or available on request.



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(Brand of dextriferron)

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In urinary tract infection

NEW "THIOSULFIL" A FORTE

alleviates the pain

controls the infection

"THIOSULFIL"-A FORTE combines the sulfonamide specific for urinary tract infection with a potent analgesic for prompt, soothing relief of local discomfort.

Recommended in acute urinary tract infection, such as cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy. "Thiosulfil" has been effective against the following urinary pathogens: Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, Streptococcus fecalis, Escherichia intermedium, and Aerobacter aerogenes. In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "Thiosulfil"-A Forte does not control the infection.

USUAL DOSAGE: Adults: 2 tablets, four times daily.

Children: (9 to 12 years): 1 tablet, four times daily.

WARNING: Due to the high solubility in body fluids of "Thiosulfil" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthemata, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazodiamino-pyridine HCl component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

SUPPLIED: "Thiosulfil"-A Forte-No. 783: Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

also available: "Thiosulfil"-A-No 784: Each tablet contains sulfamethizole 0.25 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

USUAL DOSAGE: Adults: 2 tablets, four times daily. Children: (9 to 12 years): 1 tablet, four times daily.

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Flexible Modess Tampons are designed to curve naturally below the uterusproviding complete absorbency for all lines of menstrual flow. Flexible Modess Tampons assure your patient of more protection, more comfort and more freedom.

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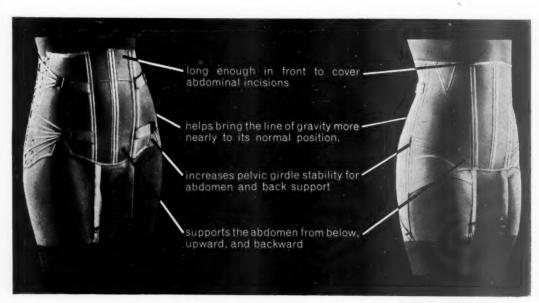
Gyne .



ABDOMINAL SUPPORTS

create a foundation about the pelvis to hold the viscera upward and backward

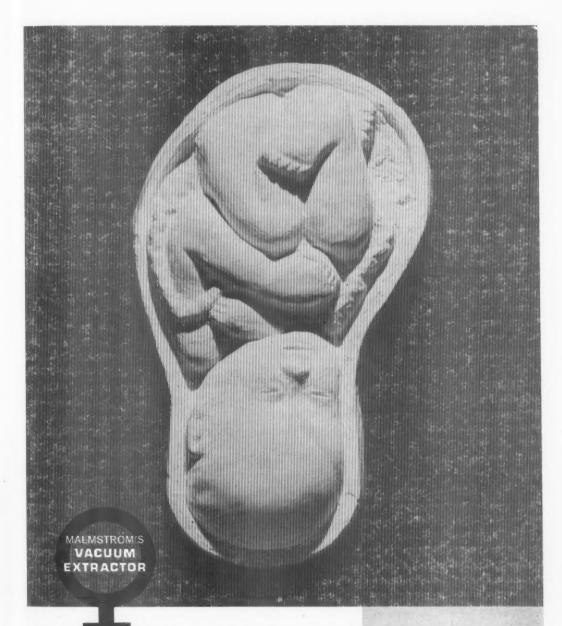
Camp abdominal supports have many varied uses for conservative treatment. Many women patients need a functional general support to help them solve a figure problem. Other patients may require a post-operative, a postnatal, a hernia support or a simple geriatric garment for their particular medical condition. The garments illustrated are two of a group in the Camp abdominal support series. Each is scientifically designed to meet the specific requirements of the patient . . . the demands of the attending physician. All of the Camp abdominal support models adequately support the abdomen, the spinal column and gluteal region without discomforting pressure. Each allows freedom of movement and is a help in preventing fatigue.



S. H. Camp and Company, Jackson, Michigan

S. H. Camp and Company of Canada, Ltd., Trenton, Ontario





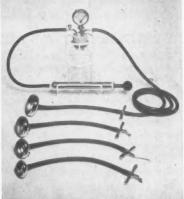
Deliveries at childbirth made with less threat to mother and child by using Malmström's new Vacuum Extractor. The highly advanced instrument induces a vacuum inside an all metal cup contacting the foetal head thereby assisting in the natural delivery without the use of forceps...used in synchronized action with uterine contractions. Because of its unique application fewer large ruptures are caused and contributes to shorter hospitalization. Significant advantages in operative deliveries and in all instances a noticeable decline in child injury and maternal morbidity.

Unit consists of hand vacuum pump, wire hanging rack, vacuum pressure gauge, vacuum bottle and 4 rubber enclosed chains with 4 sizes of suction cups.

Write for clinical study of 100 cases by O.G.A. Berggren from the Department of Obstetrics and Gynecology (G.E. Hagblom, M.D.), The Central Hospital, Linköping.

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THERAPEUTIC INDEX

"Thiosulfil" Forte 0.5 Gm.

BRAND OF SULFAMETHIZOLE

"THIOSULFIL" has been found effective against the following urinary pathogens: Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, Streptococcus fecalis, Escherichia intermedium, and Aerobacter aerogenes. In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "THIOSULFIL" FORTE does not control the infection.

INDICATIONS: Treatment of cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy; prior to and following genitourinary surgery and instrumentation; prophylactically, in patients with indwelling catheters, ureterostomies, urinary stasis, and cord bladders.

SUGGESTED RANGE OF DOSAGE: Adults: 1 or 2 tablets (0.5 Gm.-1.0 Gm.) three or four times daily.

WARNING: Due to the high solubility in body fluids of "THIOSULFIL" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthemata, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATION: A history of sulfonamide sensitivity.

SUPPLIED: NO. 786 —"THIOSULFIL" FORTE — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE—NO. 785: "THIOSULFIL"—Each tablet contains sulfamethizole 0.25 Gm. (scored), in bottles of 100 and 1,000. No. 914—"THIOSULFIL" Suspension—Each 5 cc. (teaspoonful) contains sulfamethizole 0.25 Gm., in bottles of 4 and 16 fluidounces.

SUGGESTED DOSAGES: Infants and children: The dosage is scheduled on an average basis of ½ to ¾ gr. (30 to 45 mg.) per pound of body weight per day in divided doses. Maximum dosage up to 50 lbs., ½ teaspoonful q.i.d. Maximum dosage from 50 to 75 lbs., 1 teaspoonful q.i.d.

WHEN ANALGESIA IS DESIRED

"THIOSULFIL"-A FORTE NO. 783:

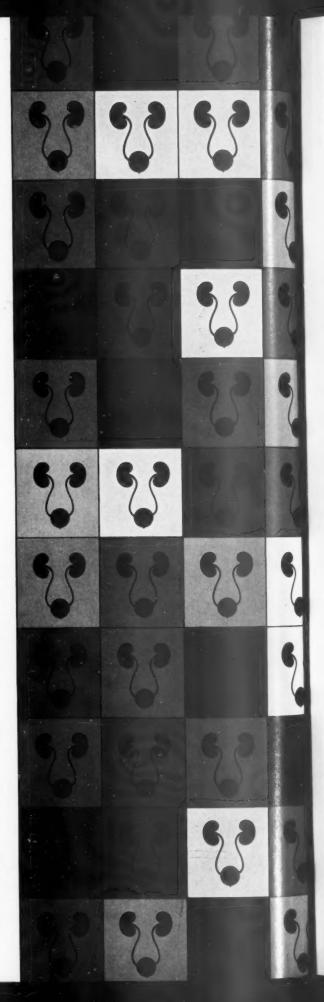
Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazo-diaminopyridine HCI component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

USUAL DOSAGE: Adults: 2 tablets, four times daily. Children (9 to 12 years): 1 tablet, four times daily.

ALSO AVAILABLE: No. 784 "THIOSULFIL"—A
—Each tablet contains sulfamethizole 0.25 Gm.,
and phenylazo-diamino-pyridine HCl 50.0 mg., in
bottles of 100 and 1,000. USUAL DOSAGE:
Adults: 2 tablets, four times daily. Children (9 to
12 years): 1 tablet, four times daily.

For references, see opposite page.



SAFELY MANAGES ALL EPISODES OF URINARY TRACT INFECTION

"Thiosulfil" Forte 0.5 Gm. Tablet

(BRAND OF SULFAMETHIZOLE

THE ONE SULFONAMIDE THAT OFFERS

- Maximum urinary concentration of active, free sulfa at site of infection
- Rapid clearance (noncumulative)
- Rare incidence of side effects
- High degree of clinical effectiveness

"Thiosulfil" dosage schedules reported in the literature.

INITIAL EPISODE (Acute Infection) 3 Gm./day1

Based on 7 years' clinical experience in treating 3,057 cases of upper and lower urinary tract infection, Bourque¹ found 3 Gm./day for 2 weeks (the average dosage employed in 97 per cent of patients) effective in most cases.

RECURRING EPISODE (Flare-up) 3 Gm./day1

Same dosage as above. When longer therapy is required as in cases where there is stasis due to obstruction, administration may be continued at a lower dosage range.

CONTINUING EPISODE (Stasis/Obstruction) 2 Gm./day^{2,3} 0.5 Gm./day⁴

Where infection remains latent due to causes which cannot be eliminated as in paraplegia, patients have been maintained symptom-free on dosage regimens ranging from 2 Gm. to 0.5 Gm./day. After initial control of acute symptoms, therapy may be continued indefinitely on a low dosage basis to guard against recurrence and prevent ascending infection. Many cases can be controlled with as little as 0.5 Gm./day.

SUPPLIED: No. 786 — "Thiosulfil" Forte — Each tablet contains sulfamethizole 0.5 Gm. (scored), in bottles of 100 and 1,000.

ALSO AVAILABLE—In urinary tract infection—to alleviate pain and control the infection: No. 783—"THIOSULFIL"®-A FORTE combines the <u>sulfonamide specific</u> for urinary tract infection with a <u>potent analgesic</u> for prompt, soothing relief of local discomfort. Each tablet contains sulfamethizole 0.5 Gm. and phenylazo-diamino-pyridine HCl 50 mg., in bottles of 100 and 1.000 tablets.

References: 1. Bourque, J.-P., and Gauthier, G-E.: L'Union Medicale 89:840 (May) 1980. 2. Cottrell, T. L. C., Rolinick, D., and Lloyd, F. A.: Rocky Mountain M. J. 58:88 (Mar.) 1959. 3. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 4. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1958.









SUCCESSFUL FAMILY PLANNING...BASED ON YOUR COUNSEL AND

LANESTA GEL

Every young couple about to be married needs advice of all sorts, and they'll get it, too — from every-body — some good, some bad. But some of the most valuable counsel they can get — help in planning their own family — comes best from you. Their family happiness for many years can depend on what you suggest to them, including your recommendation for the use of Lanesta Gel.

Lanesta Gel, with or without a diaphragm, is a most effective means of conception control. Lanesta Gel offers faster spermicidal action because it rapidly diffuses into the seminal clot. In fact, Gamble ("Spermicidal Times of Commercial Contraceptive Materials – 1959"*) found the mean diffusion spermicidal time of Lanesta Gel to be three to seven times faster than the mean diffusion times of ten leading commercially available contraceptive creams, gels, or jellies.

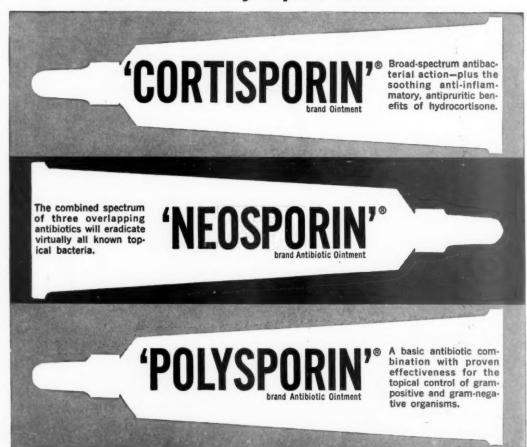
Lanesta Gel has complete esthetic acceptance and is well tolerated. "Gamble, C. P.: Am. Princi. & Digest. Treat. 11:852 (Oct.) 1990.

A PRODUCT OF LANTEEN® RESEARCH Distributed by Supplied by Esta Medical Laboratories, Inc., Alliance, Ohio BREON LABO

Distributed by BREON LABORATORIES INC., New York 18, N. Y.



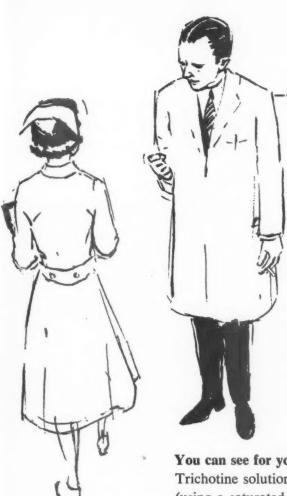
'B.W. & Co.' 'Sporin' Ointments rarely sensitize... give decisive bactericidal action for most every topical indication



Contents per Gm.	'Polysporin'®	'Neosporin'®	'Cortisporin'®			
'Aerosporin'® brand Polymyxin B Sulfate	10,000 Units	5,000 Units	5,000	Units		
Zinc Bacitracin	500 Units	400 Units	400	Units		
Neomycin Sulfate	-	5 mg.	5	mg.		
Hydrocortisone		_	10	mg.		
Supplied:	Tubes of 1 oz., ½ oz. and ½ oz. (with ophthalmic tip)	Tubes of 1 oz., ½ oz. and ½ oz. (with ophthalmic tip)	Tubes of ½ oz. and ½ oz. (with ophthalmic tip)			



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York



<u>"</u>be sure to make up more

TRICHOTINE

solution for our examining room."

You can see for yourself the efficient detergent action of Trichotine solution in reducing promptly a cervical plug (using a saturated cotton pledget), or washing away the "cheesy" exudate of monilia.

TRICHOTINE is just as effective for therapeutic irrigation by your patient at home

The same qualities — detergency, antisepsis, healing — make Trichotine ideal for the treatment of cervico-vaginitis and leukorrheas, alone or in conjunction with other antimicrobials. In the itching, burning, and foul odor of non-specific vaginitis and leukorrhea the action of Trichotine is immediate and gratifying to the patient.

The more you expect of a douche, the more you will use Trichotine in the office and prescribe it for home irrigation, and recommend it as well for postmenstrual and postcoital hygiene.

The modern detergent

SURFACE TENSION: TRICHOTINE 34 DYNES; VINEGAR 60 DYNES; TAP WATER 70 DYNE

douche

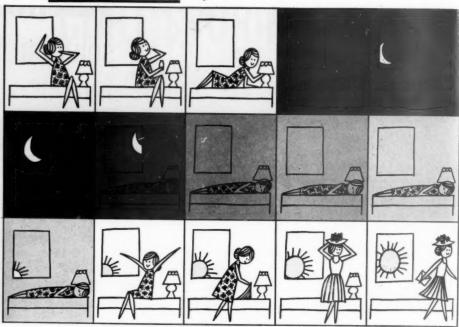
TRICHOTINE

THE FESLER COMPANY, INC. 375 Fairfield Avenue, Stamford, Conn.

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BENDECTIN

at bedtime ?



prevents
morning sickness
here!

"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating... the dose taken at night becomes effective in the morning."

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS²

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTA		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
A Section of the second		TOTA	- 11-46	

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."²

Measure Bendectin against your present Rx:

- Q. Has your present Rx been shown to relieve morning sickness before it starts in more than 9 out of 10 patients?²⁻⁵
- $Q.\ \mathrm{Is}\ \mathrm{your}\ \mathrm{present}\ \mathrm{Rx}\ \mathrm{free}\ \mathrm{of}\ \mathrm{phenothiazine}\text{-like}\ \mathrm{side}\ \mathrm{effects}\ \mathrm{and}\ \mathrm{habituating}\ \mathrm{properties}\ ?$
- Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

With Bendectin, the answer to all three is YES.

FORMULA:

DOSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

- 1. Middleton, T. F.: Postgrad, Med. 24:699, 1958,
- 2. Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.
- 3. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.
- 4. Personal communications, 1956-57.
- 5. Towne, J. E.: Internat. Rec. Med. 171:588, 1958.

 TRADEMARKS: BENDECTING, BENTYLO, DECAPRYNO



The Wm. S. Merrell Company Cincinnati, Ohio • St. Thomas, Ontario designed for all gravid patients...

particularly the multipara





Natalins tablets

Comprehensive vitamin-mineral support, pre- and post-natal

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Only one Natalins tablet per day provides generous amounts of iron, calcium, and vitamin C, plus 8 other important vitamins. This special formula helps assure, in multiparas, the extra nutritional protection they—particularly*—need. It naturally follows that this formulation will be adequate for the primigravida. With their new smooth coating, Natalins tablets are easier to swallow—and they disintegrate rapidly and fully for maximum utilization.

And for basic supplementation when her diet appears adequate, Natalins® Basic tablets provide, in one tablet a day, ample amounts of the four basic vitamins and minerals needed to guard the well-being of patient and baby.

For convenience in specification, Natalins tablets and Natalins Basic tablets have replaced all other Natalins formulations.

*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.



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Symbol of service in medicine

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nearly identical to mother's milk1 in nutritional breadth and balance

A new infant formula Enfant formula Infant formula

Five years of research and 41,000 patient days of clinical trials demonstrate the excellent performance of Enfamil. This new infant formula satisfies babies and they thrive on it. Digestive upsets are few and stool patterns are normal. Enfamil produces good weight gains. In a well-controlled institutional study² covering the crucial first 8 weeks of life, Enfamil produced average weight gains of 11.3 ounces

every 2 weeks during the course of the study. Enfamil is nearly identical to mother's milk¹
• in caloric distribution of protein, fat and carbohydrate•in vitamin content (vitamin D added in accordance with NRC recommendations)
• in osmolar load • in ratio of unsaturated to saturated fatty acids • in absence of measurable curd tension for enhanced digestibility

The Composition of Milks, Publication 254, National Academy of Sciences and National Research Council, Revised 1953.
 Brown, G.W.; Tuholski, J.M.; Sauer, L.W.; Minsk, L.D., and Rosenstern, I.: J. Pediat. 56:391 (Mar.) 1960.



Proven

in over six years of clinical use and more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- 1 simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

Miltown

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d. Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

_Also supplied in sustained-release capsules . .

Meprospan^o



Available as Meprospan-400 (blue-topped sustained-release capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped sustained-release capsules containing 200 mg. meprobamate).

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in hysterosalpingography for detecting uterine and tubal abnormalities

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BARD-PARKER STERILE BLADES

in the puncture-resistant easily opened package

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CARBON

- SHARP at equal hardness-carbon holds its cutting edge longer.
- RIGID the 'RIB'-exclusive with the B-P RIB-BACK carbon steel blade gives extra rigidity. Rolling a 'rib' on stainless is difficult and too costly.
- SAFE danger of breakage during surgery is minimized—carbon has a greater degree of toughness without embrittlement.

STAINLESS

- CORROSION RESISTANT will not corrode when subjected to a reasonable period of thermal sterilization.
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BARD-PARKER BLADES are available:

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Non-Sterille B-P RIB-BACK carbon steel (6 of one size per package)

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relief from postpartum pain



"Darvon Compound can be used as a satisfactory and effective substitute for a standard codeine-aspirin preparation in the relief of the ordinary discomforts of the postpartum period and is without significant side-effects upon either the patient or her baby."

Santiago, F. S., and Danforth, D. N.: Non-Narcotic Analgesia to Simplify Postpartum Care, Obst. & Gynec., 13:22, 1959.

DARVON® COMPOUND and DARVON COMPOUND-65

. . . combine the analgesic advantages of Darvon® with the antipyretic and anti-inflammatory benefits of A.S.A.® Compound. Darvon Compound-65 contains twice as much Darvon as regular Darvon Compound without increase in the salicylate content or the size of the Pulvule®.

Formulas:

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32 m	g.				Darvon								65 mg.
162 m	g.				Acetophene	tic	lin						162 mg.
227 m	g.				A.S.A.®								227 mg.
32.4 m	g.				Caffeine							*	32.4 mg.

Usual Dosage:

Darvon Compound: 1 or 2 Pulvules three or four times daily.

Darvon Compound-65: 1 Pulvule three or four times daily.

Darvon® Compound (dextro propoxyphene and acetylsalicylic acid compound, Lilly)
Darvon® (dextro propoxyphene hydrochloride, Lilly)

A.S.A.® Compound (acetylsalicylic acid, acetophenetidin, and caffeine, Lilly)

A.S.A.® (acetylsalicylic acid, Lilly)

120227

American Journal of Obstetrics and Gynecology

Transactions of the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society

In the pursuit of excellence

President's address

GEORGE E. JUDD, M.D.

Los Angeles, California

Foreword

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The appearance of this issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY marks an important milestone in the life of the Pacific Coast Obstetrical and Gynecological Society. This initiates what we confidently hope will be the beginning of many yearly presentations of our transactions to the discriminating readers of this outstanding publication. We take quiet pride in being included among those national and regional sponsoring societies whose transactions have appeared yearly, and we look forward to the opportunity of joining our strength with theirs for the improvement of obstetrics and gynecology.

There may be some who would be interested to learn that the Pacific Coast Society came into being in the fall of 1931 at an

organization meeting sponsored by the leaders in obstetrics and gynecology of the various regions of the Pacific Coast. The chairman of the Organizing Committee was Albert Mathieu of Portland, Oregon; the first president was Frank Lynch of San Francisco. The interested reader is referred to the special article "In the Beginning" by William Benbow Thompson, appearing in the *Transactions* of 1956, for further details. This article describes in pungent and whimsical style the early activities and meetings of the Society.

Except for the war years of 1944 and 1945, scientific meetings have been held every year since the Society's "beginning." This thirtieth year since the founding of the Society and the initiation of our first *Transactions* in this publication offer the opportunity to ponder our past and review the ways wherein we can "contribute to the greatness and strength of a free society" by the pursuit of excellence within our field of endeavor.

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960.

ELECTION to the presidency of this beloved Society is an honor that transcends any I have ever received or hope to have conferred upon me. May I express to each of you my sincere appreciation for this signal recognition.

With every honor go great responsibilities, the greatest being the obligation to add, if possible, to the accomplishments of the past. Further accomplishment may best be guaranteed by meeting the challenge of the present and appraising our future needs and problems.

A review of Dr. William Benbow Thompson's "In the Beginning" clearly indicates that this Society was founded by wise and congenial men, out of their need for an opportunity to gather together, exchange views, increase their knowledge, and enjoy a communion of understanding and friendship dedicated to the improvement of obstetrics and gynecology in the West.

To each of us, membership in the Pacific Coast Society has meant a prized goal, an achievement. It has offered an opportunity each year for a review and a reappraisal of the basic knowledge of our specialty; we reassess our objectives and clarify and redefine our ideas in the forum of presentation and discussion. We have created bonds of understanding, unity, and friendship that could not be achieved otherwise. Certainly, in the minds of most of us, regardless of other fortunate associations, this Society comes first in our hearts. Membership has been for each of us an important steppingstone in moving upward, and it is gratifying to note how often national recognition has come to so many members of our Pacific Coast Society.

This thirtieth year since the founding of our Society offers an opportunity to pause and to ponder the past, view the present, and project the future. May I humbly share my thoughts with you, with the hope that they may be constructive for the present and promote a better future in our "Unity and Friendship" in the Pacific Coast Society.

Looking backward, we can be proud of

many past accomplishments. In 1934 the "Seven Cities Maternal Mortality Report by Bell, Watkins, O'Shea, Page, Stephenson, Thompson, and Weir furnished one of the most complete, most highly regarded, and most frequently quoted surveys on the subject of maternal mortality. This report together with the New York City, the Philadelphia, and the Fifteen States Study certainly defined the areas where improvement in maternal care needed to be made. Reduction in the maternal mortality rate in the past 25 years has been one of the great accomplishments of modern medicine.

The Chorionepithelioma Registry, under the stewardship of the American Association of Obstetricians and Gynecologists—while not an accomplishment of our Society—stemmed from a trio of 5 year reports on chorionepithelioma by Mathieu and Holman presented to this Society. Albert W. Holman, our seventeenth president, gave the initial funds establishing this Registry, doing so in the name of Mathieu, our second president. In the forum of our meetings and through action of our members, this valuable agency was given birth.

The Frank Lynch Memorial Lecture has served to encourage many young men in research, offering them an opportunity to present their results before a well-informed audience.

The influence of our members upon local hospital staffs and local obstetrical and gynecological societies as a result of our scientific sessions cannot be gauged; however, it has been significant. Today our Society enjoys the respect and regard of the other regional and national societies, thanks to its past achievements and the high caliber of its membership. This brief accounting of the past is for the purpose of establishing a point and perspective from which we may look to the future.

Our Constitution expresses our objectives as committing us to "the advancement of knowledge of all matters pertaining to the practice of obstetrics and gynecology." This pronouncement encourages a broad review of

the challenges that lie ahead. Osler warned if a complacent attitude when he noted:

Schools and systems have flourished and gone, schools which have swayed for generations the thoughts of our guild and systems that have died before their founders. The philosophies of one age may become the absurdities of the next and the foolishness of yesterday has become the wisdom of temorrow through long ages which were slowly learning what we are hurrying to forget.

The spirit of our time seems to be that of reappraisal, and in this the leaders of medicine, and particularly those in obstetrics-gynecology, have expressed clearly their concerns for our future. They have emphasized tasks that need to be done and areas where improvements in patient care are indicated.

To realize that our present conditions will certainly change, we need only to appreciate the projected numbers of doctors of medicine necessary to provide adequate care for patients by the year 1975. The Surgeon General's Consultant Group on Medical Education and the Western Interstate Commission of Higher Education both stress the prodigious tasks ahead for American medical education. In brief, in this country, we must in just 15 years increase our medical school graduates from our present 6,895 to 11,000 -an increase of more than 3,000. In particular, the West must provide doctors for 40 million people—an increase of 17 million over our present population. In this atmosphere of growth and expansion the end product of our training programs in obstetrics-gynecology must be improved.

Here are some of the valuable and essential areas of improvement that have been pointed out to us. Our own Daniel G. Morton, speaking before the Central Association of Obstetricians and Gynecologists, called attention to our heterogenous training programs and the lack of uniform quality in our standards of practice. He concluded:

While obviously there is no one road to wisdom and learning, this picture of what is offered for the education of the obstetrician-gynecologist today leaves much to be desired.

Morton further pointed out the value and

importance of the support of our national societies in developing improved training programs. George W. Gardner, in a recent survey, indicated obstetrics and gynecology does not receive its proportionate share of students who are rated in the upper group of the graduating classes. The late Herbert E. Schmitz in his Presidential Address to the Central Association expressed concern over the division of responsibility for treatment of female genital cancer; he enlisted the support of his organization, of the American College of Obstetricians and Gynecologists, and of sister societies in improving the cancer-training programs. Axel N. Arneson, a year later in a similar address before the same Association, outlined a thoughtfully conceived program to be applied at the postgraduate education level for the needed improvement. Howard C. Taylor, Jr., in addressing the American Gynecological Society as President, indicated the numerous areas of overlap between our specialty and others and emphasized the wide range of knowledge required in our practice, outlining his views on ways and means to improve patient care. This same thesis was further discussed by John I. Brewer in his Presidential Address before the American College of Obstetricians and Gynecologists under the appropriate title, "Better Fences Make Better Neighbors." Brewer suggested a study by a committee of general surgeons, urologists, radiologists, and other concerned specialists for agreements to be applied at the graduate training level. William F. Mengert in his Presidential Address before the American Association of Obstetricians and Gynecologists offered an appraisal of our specialty today. After recounting our problems both from within and from without, he issued a challenge for an improvement in the product of our training programs and expressed the hope that the product be "the woman's doctor," a competent specialist "with potential to be a force for improvement in the profession and his community."

The concerns expressed by these leaders and their suggestions should be a challenge to every obstetrical-gynecological society, and

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ectives ent of to tile "This view of particularly to our Society. We should be leaders in our geographical area and lend willing and active support to other societies in furthering all these worthy goals. To quote Mengert, these goals "will require vision and a willingness to think and act cooperatively on a national scale." In this vision and willingness to think and act cooperatively, we must be sure the Pacific Coast Society will be in the vanguard of leadership.

Before closing this address, may I add one more item to the suggestions reviewed, hoping for further improvement in graduate training of obstetricians-gynecologists of the future.

During the past 5 years I have had the opportunity of reviewing a significant number of cases involving litigation arising out of obstetrical or gynecological care. The information regarding these cases was developed by a trained investigator who painstakingly interviewed all personnel involved doctors, nurses, attendants, patients, and families. The total scope of his experience would involve about 500 cases, of which 51 concerned obstetrics or gynecology. A detailed critical review of these 51 cases would be out of place in this presentation; however, there are certain observations that seem worthy of discussion based upon a thoughtful analysis of these reports.

It is reasonable to assume that the ultimate degree of patient dissatisfaction is represented by the filing of a suit; however, lesser degrees of the breakdown of patient-doctor relations exist in which initiation of legal proceedings never occurs—the patient simply seeks a new doctor. To be sure, there are some cases where nothing could have been done to avoid dissatisfaction, i.e., no failure was found in the performance of the doctor in his care or management. There were other cases where skilled care and interest settled difficult problems that arose in patient care without recourse to the courts. These latter represent the results of well-trained, interested, and friendly doctors applying their best efforts in the art and science of medicine.

There were about 40 per cent of the cases

that seemed to point to physician failure—not in technical skill or ability but rather in failure of the doctor in his personal relationship with his patients or the family Significantly, the Board-certified doctor wainvolved about half the time. The possible provocative motives were summarized after a critical review of all the information, and a partial list of these summaries follows:

- 1. Lack of candor in explanation of complications.
- 2. Lack of concern for patient's feelings or welfare.
- 3. "Flippancy" and poor taste regarding personal problems of patients.
- 4. Delay in imparting important information.
 - 5. Anger instead of a logical explanation.
 - 6. Impetuosity.
 - 7. Arrogance.
- 8. Lack of serious attitude toward major problems of the patient.

Various combinations of these possible etiological incidents or attitudes occurred in some of the cases. The interview with these disenchanted patients often pointed to a critical event in the patient-doctor relationship when, with one or more of these provocative occurrences or responses, the deterioration of confidence in and respect for the doctor began. Frequently these incidents occurred some time prior to the severance of professional relations or the initiation of legal proceedings.

Recounting of these unpleasant circumstances is not for the purpose of avoiding legal entanglements. I believe, however, they point to a basic failure of attitude on the part of these doctors toward their patient and a failure of understanding the feelings and reactions of the ill patient.

Understanding the status of the patient has been described by many. Flanders Dunbar says:

Patients come in hurt, frightened, angry, confused, sometimes demanding, defiant, or in despair. They forget, they misrepresent, they lie, they digress, and they cry or they are interminably reasonable, factually conscientious, and polite. The first task is not history but the establishment of communication.

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This is particularly true of the obstetrical and gynecological patient who must seek relief for her problems in an anatomical region related to the most intimate and personal aspects of her life and one that from early childhood has had deep and significant associations with her emotional make-up. She is often embarrassed and distressed and consequently hostile at the necessity of examination and of confiding vital information perhaps never shared with any other person.

The obstetrical patient presents the impact of the instinctual drive of motherhood with all its ambivalent forces. This impact is felt in greater or lesser degree by all patients and often is one of the basic difficulties in personality disturbances seen during pregnancy and in emotional illnesses. With the interplay of these emotional forces she can be easily offended by thoughtless, facetious or disparaging remarks. She is particularly piqued when she may find a lack of concern or sincerity in the doctor-patient relationship or if she has a feeling that she as a person does not command wholesome respect from her doctor. The real art of the practice is not equated to the development of a winning personality but to the basic desire to help a human being in distress with patience, candor, and understanding. Osler cautioned of this problem:

As the practice of medicine is not a business, the education of the heart, the moral side of man, must keep pace with the education of the head; our fellow creatures cannot be dealt with as a man deals in corn or coal. The human heart by which we live must control our professional relations. After all, the personal equation has most to do with the success or failure in medicine and in the trials of life the fire which strengthens and tempers the metal of one softens and ruins another.

The true art of the practice of medicine must once more become a part of the training curriculum. It must be distinguished from the oft-deplored smooth bedside manner which is divorced from the excellence of technical skills, knowledge, and judgment. It might be defined, in part, as a human understanding of the plight of the female patient as she presents herself for medical

care; the application of honor and sincerity in all communications, the avoidance of the emotional problems of the doctor himself entering into the patient-doctor relationship, and the practice of the credo: "To cure sometimes, to relieve often, to comfort always."

When and where should the doctor receive instruction regarding this important aspect of doctor-patient relations? Helen Hofer Gee, in a questionnaire to graduates out of medical school 10 years, found 42 per cent thought their medical school experience deficient in this category. Two thirds felt that the internship provided good or excellent facilities for learning these skills, and 83 per cent who had residency or fellowship experience rated good or excellent their opportunities for developing understanding and skills of vital doctor-patient relationship. Residency training programs have been an important factor in the education of the doctor in this regard; however, it would appear that greater efforts are necessary in the future if we are to reach the ideal.

An observation made by the intelligent medical investigator, whose findings were reviewed, seems to me of great significance: "Doctors have often said 'What could I have done differently in the treatment of this case?" but never 'What did I do personally to bring on this problem?" "Recognition that what we do in our personal relations with patients is as important as what we do with our technical skills and knowledge is vital for the best of the art and science in the practice of obstetrics-gynecology.

In the pursuit of excellence for this Society, we must recognize that the great purpose for our beginning and present existence is the "improvement of all matters pertaining to the practice of obstetrics and gynecology." This is a continuing activity that calls for vigor, vision, and enthusiasm. It requires cooperation with other similarly dedicated societies to bring about the desired improvements. Periodically, reappraisal and re-examination of goals and purposes are essential to avoid complacency and indifference.

For the development of excellence in our practitioners of the future we must continue to advance the technical skills and incorporate the scientific achievements which have brought so much relief from distress to our patients; however, in bringing about this excellence we must recognize the importance of the art of the practice of medicine as it relates to the sympathetic rapport with the distressed patient. The development of the art of the practice will be obtained only by inculcating in all training programs the importance of the basic understanding of the distressed patient and the development of attitudes as physicians toward this patient which is born of wisdom and compassion. When this art is integrated with the best technical skills and knowledge in our specialty, we will approach the degree of excellence that should be our goal.

An unknown writer has left this gem which may serve as an epilogue:

The illustrious ancients when they wished o make clear and to propagate the highest virtus in the world, put their states in order. Before pulting their states in proper order, they regulat d their own families. Before regulating their families, they cultivated their own selves. Before cultivating their own selves, they perfected their souls. Before perfecting their souls, they tried to be sincere in their thoughts. Before trying to be sincere n their thoughts, they extended to the utmost their knowledge. Such extension of knowledge lay in the investigation of things and seeing them as they really were. When things were thus investigated, knowledge became complete. When knowledge was complete, their thoughts became sincere. When their thoughts became sincere, their souls became perfect. When their souls were perfect, their own selves became cultivated. When their selves were cultivated, their families became regulated. When their families were regulated, their states came to be put in order. When their states were in proper order, the whole world became peaceful and happy.

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Public relations in our maternity wards

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The time-honored goal of obstetricians is to make childbirth safe. And safety, expressed in terms of fetal and maternal mortality, is our usual yardstick for measuring the quality of obstetrical care. Our patients, however, are likely to use a different yardstick. Accepting today's safety as their just due, patients tend to judge the quality of their obstetrical care in terms of comfort and in terms of the amount of attention they receive from their doctors and from hospital personnel.

Ideally, every childbirth experience should be a happy and satisfying event, as well as a safe one. However, those of us who practice obstetrics know that for many reasons, more or less beyond our control, the hospital experiences of some of our patients fall far short of this ideal. It is an enigma of modern obstetrics that what passes in the record as a normal labor and delivery may be bitterly remembered by our patient as a terrifying experience.

Doctors, and the hospital services they help to direct, have been publicly attacked in lay magazine articles because of these shortcomings. Titles include phrases such as, "Cruelty in Maternity Wards," or, "Can You Trust Your Obstetrician?" Such articles, especially those apparently written from collections of letters from dissatisfied patients, are frightening for prospective mothers to read. They are of concern to all physicians interested in improving medical public relations. They are read with defensive resentment by responsible obstetricians who know that obstetrical safety and obstetrical comfort are not always parallel, but nevertheless can recognize an element of truth in the accusations.

It is not easy to evaluate the true situation which must lie somewhere between the emotion-tinged reports of dissatisfied patients and the ruffled feelings of obstetricians who are diligently continuing the reduction of fetal and maternal mortality. Are a significant number of patients leaving our hospitals with emotional injuries and resentment against the medical profession? Are there ways we could improve the comfort and happiness of the hospital childbirth experience, without sacrifices in safety and cost?

The purpose of the present study is to obtain a measure of the gap that seems to lie between the ideal and what actually happens, in typical metropolitan hospitals, as seen through the patient's eyes. From it we hope to devise ways to improve the comfort and satisfaction of our obstetrical patients. Pleased obstetrical patients will improve hospital and medical public relations. Furthermore, as insurance companies have learned, people who are pleased with kindness and consideration shown them by medical aides, are reluctant to bring medicolegal claims against either doctors or hospitals.

From the Department of Obstetrics and Gynecology, Mercy Hospital, and the Section on Obstetrics and Gynecology, The Donald N. Sharp Memorial Hospital.

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960.

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Method and material

A questionnaire survey of hospital experiences was conducted among all of our partnership private patients who were delivered during the past 5 years. All but 1 per cent were delivered in two San Diego hospitals, Mercy Hospital and Sharp Hospital, hereinafter called "Hospital A" and "Hospital B."

Mercy Hospital is a large private general hospital with an organized intern and residency program. The obstetrical service averages more than 5,000 deliveries each year. Sharp Hospital is relatively new, with a modern decor, and averages over 3,000 deliveries each year. Both hospitals are often filled to more than capacity. Both have new obstetrical units in the process of planning or construction.

The questionnaire was constructed so that each patient could grade her own care at each stage in the hospital experience: (1) entering the hospital; (2) labor and birth; (3) postpartum care; (4) receiving the bill. Ample space was provided for the candid comments that were requested.

Patients were asked what they liked best, and what they most disliked about the way they were treated. Finally, they were asked for their own suggestions which could be used to improve hospital care.

Of the 1,886 questionnaires mailed, two thirds, or 1,048 were returned. Sixty-two per cent were from former Mercy Hospital patients; 37 per cent were from former Sharp Memorial Hospital patients. Some patients had more than one maternity hospital experience during this time period. In evaluating the results, only the most recent experiences were considered.

The questionnaires, as they were returned, were studied first by ourselves and then by the administrator of each hospital. They were then subjected to statistical analysis and to psychological interpretation by Dr. Oscar Kaplan, Professor of Psychology, San Diego State College.

Results

1. Entering the hospital. The first question and patient replies follow:

"How were you received as you entered the hospital?"

	Hospital A	Hospital B
Warmly	74%	83%
"So-so"	23%	16%
Coldly	3%	1%

Although very few patients stated they were received coldly, approximately 25 per cent felt their reception was not what it should have been. Remarks from the 25 per cent were studied and the great majority from each hospital who complained felt they were received in a routine, indifferent, businesslike manner. Remarks of many held praise, but room for improvement is apparent. Every patient should be received warmly.

Typical verbatim remarks are now proving helpful in personnel retraining:

 "Everyone was most efficient; however, a little more friendliness would have been appreciated."

2. "They acted as if they were doing me a favor by signing me up."

3. "The nurses who received me were friendly and showed a genuine interest. This put me at ease."

2. Labor. Our next question was concerned with labor. With all that can happen in a busy labor room, it was here we expected the greatest number of complaints. Surprisingly, the reverse was true. Many patients seemed to feel that they received their best care and treatment from the nurses during labor.

"How were you treated by the nurses during labor?"

	Hospital A	Hospital B
Well treated	85%	82%
"So-so"	9%	12%
Poorly	3%	3%
Did not go into labor (cesarean, born on		
etc.)	3%	3%

Derogatory remarks were studied and broken down, as follows:

1.	Nurse described as	Hospital A	Hospital B
	unsympathetic, abrupt,	45.0%	2001

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2. Patient neglected during labor; nurses		
too busy for proper care	35%	36%
 Nurses indifferent, aloof, doing job routinely 	11%	18%
4 Nurse performed painful rectal examinations	11%	9%
5. Nurses made errors i judgment, doctors n		
called soon enough 6. No assurance given	2%	7%
anxious patient	2%	7%

Sample comments illustrate patients' experiences during labor and are useful in personnel training:

1. "As the nurse was getting me ready she was all business, but yet she took time to soothe me and tell me that everything would be all right."

2. "There was one nurse that was curt and short-tempered, but the rest were very nice."

3. "They yelled at me to be quiet because they could hear me in the hall. I hated them, and I'm sure they hated me."

4. "All the nurses were wonderful and helpful, explaining how and why they were doing things."

3. Postpartum care. The next question reported treatment after the birth of the baby.

"How were you treated by the nurses after the birth?"

	Hospital A	Hospital B
Well treated	81%	90%
"So-so"	14%	7%
Poorly	5%	3%
Loonly	3 /0	3 /0

A great majority of patients felt that they had good treatment after the birth of the baby. Many made warm statements of praise. But about 20 per cent in one hospital and 10 per cent in the other felt that their treatment was not what it should have been. Complaints were broken down as follows:

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1.	Patient felt neglected;		
	hospital understaffed,	0	
	service slow	56%	63%

2.	Nurses unpleasant, rude, sarcastic, reluctant to		
	give service	32%	31%
3.	Nurses indifferent, treat- ment routine or assembly		
	line	12%	6%

Verbatim comments illustrate patients' experiences after the birth of the baby:

1. "They were obviously too busy to give more than perfunctory attention."

2. "Some of the nurses were very nice. Most of them were just ordinary and some seemed to resent being there."

3. "No one ever told me the hospital rules. They just reprimanded me and others when we disobeyed them."

4. "There was one unfeeling, unsympathetic, disinterested nurse. The others were lovely. Why is there always one on every floor?"

4. The hospital bill. "What was your impression of the hospital bill and the way it was presented?"

	Hospital A	Hospital B
Good	66%	74%
Indifferent	26%	21%
Bad	8%	5%

There were a number of complaints about the bill, even by those who checked "good" on their questionnaires. Most frequent complaints were as follows:

		Hospital A	Hospital B
1.	Hospital care too expensive	28%	33%
2.	Patient felt pressured to pay, using words		
	like "bail," "hock"	12%	27%
3.	Resented "extras" on		
	bill	8%	13%
4.	Bill more than es- timated	10%	5%
5.	Resented prepayment of bill	7%	0%

Sample comments illustrate patient's impressions:

1. "The bill was far too high for maternity. I would like to see ambulatory patients get a break in the bill. I have read about this new system."

2. "The subject was brought up at the mothers' tea, so I was prepared for the bill."

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- 3. "I didn't feel overcharged because the food was good."
 - 5. Additional impressions.
- A. "What did you like best about the hospital?"

	Hospital A	H	ospital E
Food; its variety, at-			
tractive service	24%		54%
Personnel; friendly, helpful	1 34%		34%
Pleasant, bright sur-			
soundings	1%	:	39%
Care; efficient and prompt	12%		15%
Appreciated husband in			
labor room	6%		6%

Many more or less isolated comments and compliments were received in answer to this question. Many of them referred to recent improvements in hospital equipment and hospital policy. Telephones next to the bed, intercom system, daily shower, between meal snacks, and hospital cleanliness were appreciated.

Verbatim comments illustrate what patients liked best about the hospital.

- 1. "I liked the immediate answering of the buzzer, the help with the bath, alcohol rubs, lovely treatment by all, and husbands allowed in the labor room."
- 2. "I liked the food! After nine months of dieting, the more and richer, the better."
- 3. "They let you sleep late, brought coffee before breakfast, served meals at decent hours, afternoon snacks, nice nurse, showers, choice of meals and drinks—I didn't want to go home."
 - B. "What did you most dislike?"

	Hospital A	Hospital B
Nothing disliked	28%	34%
Disliked food	12%	0%
Infant visiting policy	11%	10%
Unpleasant personnel	9%	8%
Patient neglected	8%	8%

There were many more individual comments and complaints given in answer to this question. A large proportion appear to be based on minor slip-ups in usual hospital routine and in personnel-patient relations.

Sample comments to illustrate what patients most disliked about the hospital:

1. "I didn't like getting up at 5:30 A.M.

- and then waiting two and a half hours for breakfast to be served. I also didn't like boing awakened for a sleeping pill."
- 2. "My baby wasn't brought to me unt! twenty-two and a half hours after birth."
- 3. "I disliked not being permitted to bottle-feed my baby. Because I wasn't nursing, I could see the baby only once a day. He was fed in the nursery."
- 4. "I disliked the routine. The hospital must run for the benefit of efficiency, and God help the poor patient caught in the jaws of a machine that starts at 5:00 A.M. to the clatter of wash basins, and steams inexorably through the day with 77 bus boys, charwomen, Nurses Aides, Gray Ladies, etc., ad nauseam, ad infinitum, running in and out."
- 5. "I most disliked the fact that two women are in each labor room. Women who are unprepared to face the discomforts of labor frighten women who are having their first child and lead them to believe that they, too, will eventually get to the screaming stage. It is hard for someone who is trying to control herself during labor to have constant screaming in the same room with her."
- C. "Have you any suggestions that would improve your hospital care next time?"

Patients contributed many suggestions that, while they almost go without saying, still are helpful in planning our new obstetrical units and in personnel training.

Illustrative verbatim comments:

- 1. "There should be a radio or TV in the labor room."
- 2. "Nurses in the labor room should have frequent rests, to prevent short temper due to fatigue."
- 3. "Permit mothers to see infants as soon after delivery as possible."
- 4. "Have a rooming-in arrangement for the mother and child."
- 5. "Patients who have had long labors should be given food shortly after delivery, even if the kitchen is closed."
- 6. "Coffee should be served to fathers who are waiting."
- 7. "Night nurses should move around quietly."

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- 8. "Husbands should be permitted to visit freely and stay long periods of time."
- 9. "Have folding doors instead of curtains between beds."
- 10. "Mothers who have had no postpartum difficulties should have a hotel-like atmosphere; they are not ill, just resting."
- 11. "Hospitals should examine their routines and decide whether tradition or logic governs their operation."
- 12. "Hospital routine should be planned to permit more rest for the mother."

Comment

It is apparent that most obstetrical patients today accept the safety of having a baby, of which we are justly proud, without any special credit to the medical profession which is responsible. Patients tend to judge the quality of their obstetrical care in terms of comfort and the amount of attention they receive from their doctors and from the hospital personnel.

No patient reported that she lost her child due to inefficiency or neglect. The damage that was done seemed to be all psychological. Actually, there were far fewer complaints and criticisms than we had expected, particularly since both hospitals have been operating at higher capacity than was ever intended when they were designed. On the other hand, it is apparent that much can be done to improve each patient's chances of experiencing a really happy hospital childbirth.

Some women were not received warmly when they entered the hospital. It is indeed a discouraging experience to be met with bored indifference on one of the most important days of one's life. One patient stated it very well when she wrote, "Babies may be born every day of the week, but not MY baby." A need for careful selection, additional training, and constant supervision of admitting personnel seems apparent in both hospitals.

We were surprised to find that many patients considered their best treatment was during the course of labor. With all of the sudden surprises that do occur during seem-

ingly normal labor, with difficulties in controlling pain in unprepared patients, we had expected to find the severest criticisms during this period of the hospital experience. However, there appears to be room for improvement of the patients' experiences during labor. No labor nurse should ever be described as sarcastic, hostile, scolding, or impatient. Repeated comments indicated that one nurse alone created difficulties, while all the rest of the nurses were helpful and pleasant.

The postpartum period seemed to elicit the greatest number of criticisms, comments, and suggestions. Here again, one single member of the nursing or aide personnel frequently destroys all of the happy atmosphere and good relations built up by all of the rest of the personnel. From the "cold wash cloth at dawn," through the day, a thorough review of hospital procedures during the postpartum period seems indicated. Perhaps for nurses there should be more nursing and less charting, and for patients there should be regular periods set aside for quiet rest. As Norman Miller has forcefully pointed out, postpartum patients usually do not get enough rest. Tired patients are irritable and sensitive. Tired nurses are irritable. Clashes must be guarded against.

The questionnaire and the large pool of patient comments have proved helpful in many ways. The questionnaire itself seemed to serve as a step in good medical public relations, since it indicated to the patient her doctor's concern over her feelings and her welfare.

A hospital staff committee on public relations has been formed at Mercy Hospital. A director of public relations has been added to the administrative staff. Material from the questionnaire is being used in special seminars for nurses. Critical remarks from the questionnaire serve as reminders, and appreciative comments serve as rewards, in teaching personnel the art of pleasing patients. The School of Nursing is finding helpful information in improving training of student nurses. The hospital administrators and department heads have

found a great deal of helpful material which is being used in planning the decor and the operation of the new obstetrical wings now under construction. Each hospital benefited by studying comments from patients in the other hospital.

In an atmosphere of extra-friendly employees, it becomes very difficult for the patient to be hostile or uncooperative. Quoting from an insurance committee report to doctors, concerning malpractice insurance: "We have had innumerable reports where there appeared to be some justification for a possible claim against the doctor, in which the patient has mentioned to the company claims adjuster his desire to avoid any legal action because the doctor and the office personnel are so friendly and courteous to me."

Summary and conclusions

Our questionnaire survey reported the hospital childbirth experiences of more than

Discussion

DR. LEON Fox, San Jose, California. Our own survey in San Jose Hospital where we have averaged 4,300 deliveries per year in the last 2 years in facilities designed for half this number compares with the San Diego experience. Both of these areas have crowded facilities which tend to eliminate the competitive spirit between hospitals.

To cope with these problems we have evaluated our patients' complaints as well as our physicians' and nurses' observations and have accomplished the following:

- 1. A committee of hospital personnel, administration and physician, known as the "Committee for the Improvement of Patient Care" has been established and has been given authority to act. Medical staff, administration, nursing, house-keeping, and patients' problems are evaluated and acted upon.
- 2. A telephone-dictating system has been instituted to record all complaints by anyone at any phone station in the hospital. These complaints go to the above committee for evaluation and action.
 - 3. Private labor rooms are a reality.

1,000 private patients who were delivered in two San Diego general hospitals during the past 5 years.

The great majority of patients seemed satisfied with their hospital care in each of four stages of hospital experience. No patient reported loss of her baby or physical injury because of neglect or poor care. Bitter criticisms of cruelty and neglect, reported in popular magazines, were not confirmed.

A majority of complaints were found to stem from poor personnel-patient relationships. At least half the complaints can be considered preventable.

Personnel need training in the art of being warm and friendly toward patients. With such a training program, more patients will achieve our goal of a happy, as well as safe, childbirth experience.

Happier mothers will result in improved public relations for hospitals and for the medical profession as well.

- 4. A puerperal Recovery Room is functioning 24 hours daily with great satisfaction.
- 5. Delivery rooms have been air-conditioned. (We should do the same in our labor rooms.)
- 6. Intercoms in labor, delivery, and postpartum areas save many steps and please patients.
- 7. The patient sees her baby with her husband immediately after delivery, before going to the recovery room.
- 8. TV and comfort conveniences are in the fathers' waiting room.
- 9. Telephones are in the patients' rooms unless the physician orders otherwise.
- 10. Adequate showers are available for ambulatory patients.
- 11. Full anesthesiology coverage is available 24 hours daily (M.D. anesthesiologists and their own employed R.N. anesthetists).
- 12. There is an active auxiliary with "Pink Ladies" receiving patients, accompanying patients to labor suites; providing coffee and sea for fathers and patients; providing newspapers, toilet articles, flowers, etc., for patients.
 - 13. A continual training program is carried on

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for nursing personnel, auxiliary and house staff, on newer methods, patient complaints, physician complaints, and other similar problems.

14. Medical Society cooperation is obtained in urging all nursing training programs in colleges, junior colleges, and hospitals to improve not only quantity but quality when possible.

15. Medical Society participation is obtained in urging hospital building programs at every opportunity. We now have two new hospitals being completed and one in the planning stage.

16. Registered nurses are being replaced with clerks, aides, and technicians in areas where nursing knowledge is being wasted on menial and clerical duties.

We're still overcrowded, inadequately staffed, and in need of modernization of many of our wards, but our Committee on the Improvement of Patient Care has a grasp of the situation and our patients are presenting fewer complaints.

DR. MARTIN (Closing). Just as medical public relations depend basically on the total of all the day-by-day doctor-patient relationships, hospital public relations depend basically on personnel-patient relationships. Our study has revealed room for improvement. Patients do not expect to pay \$30 a day to be berated by nurses. Perhaps a public relations course for nurses and other personnel should be included in the organization of every hospital.

Spontaneous premature rupture of the membranes

MELVIN W. BREESE, M.D.

Portland, Oregon

ALL obstetricians are confronted with the problems concerned with spontaneous premature rupture of the fetal membranes. By definition this complication of pregnancy is limited to those cases, regardless of length of gestation, in which spontaneous rupture of the membranes occurs more than one hour before the onset of labor. In this study it is further limited by elimination of all cases in which the fetus was thought to be dead at the time of rupture and all cases in which a so-called high leak or questionable rupture (amniochorionic leak) was followed by a spontaneous or artificial rupture of the membranes during the subsequent labor. This latter group of cases of questionable rupture was eliminated after a review showed these do not present the problems of premature labor and perinatal mortality as do the cases of frank or complete rupture; their inclusion would distort the analysis and might well lead to unwarranted optimism regarding the seriousness of the problem.

The precise diagnosis of ruptured membranes therefore becomes obviously important. Observation of the actual continued fluid loss from the vagina by the obstetrician is of first importance. The characteristic odor and the water-like vaginal fluid containing flecks of vernix caseosa and occasionally meconium are well known to experienced

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Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. observers. Various methods of determining pH, techniques for demonstrating fat droplets in the fluid, crystallization tests (palm leaf reaction) of the fluid, and microscopic demonstration of lanugo hairs and of fetal epithelial cells in vaginal smears are some of the methods used to establish or confirm the diagnosis. 15, 16, 23

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The etiology of spontaneous premature rupture of the membranes is unknown. Hyalin degeneration and inflammatory changes have been shown to be present at the point of rupture in such cases. 14, 16, 19 It has also been shown that imbibition of the amniochorial mesoderm often with complete detachment of the epithelial lining from the underlying connective tissue and distinct dissociation of the fibrillary network is frequently present at the point of rupture.8, 18 When one reviews the microscopic anatomy of the fetal membranes, so well presented recently by Bourne,6 the possibility of congenital weakness in the structure of the membranes as well as the potential effect of inflammation seems very real. An important recent study¹⁹ included 536 determinations of the resistance to rupture of the fetal membranes with use of a plexiglas pressure chamber. It was shown that the strength of the membranes is less in premature rupture than in rupture during labor and greatest in patients with delayed rupture. It was noted also that membranes which required greatest pressures were usually pure amnion and that the more rapidly the increasing pressure was applied to all membranes the less was the pressure required to produce rupture. This ist observation would tend to explain the role of uterine and intraperitoneal pressure changes which might prematurely rupture otherwise normal membranes.

A most interesting thought was recently suggested by Behrman and associates⁴ on the possibility of ABO(H) blood incompatibility between fetus and mother as a cause of congenitally poor fetal tissues such as the membranes. I know of no study investigating this possibility, but it is intriguing.

The possible phenomena related to this complication have been previously studied.^{3, 5, 7, 10, 11, 12, 20, 22, 25, 27, 29} There is a difference of opinion as to whether maternal morbidity is significantly affected, but increased perinatal mortality is unquestioned. The role of antimicrobial therapy is questioned by many authors. Antibiotics apparently are used widely, however.

The purpose of this study is to analyze the factors related to spontaneous premature rupture of the membranes as defined above in pregnancies producing premature infants. Infants weighing 501 to 2,500 grams at birth were considered premature. The limitations of this arbitrary category are recognized.

Material

During the 10 years (1950 to 1959, inclusive) there were 44,723 deliveries at Emanuel Hospital, a private general hospital. Of these, the membranes ruptured spontaneously more than one hour before the onset of labor in 2,887, an incidence of approximately 1 in 16 deliveries (6.4 per cent). Of the patients sustaining this complication 515 were delivered of premature babies, roughly per cent of all the patients delivered (Table I). This study is concerned with these 515 mothers and their infants. In the cases of multiple pregnancy only the infant whose membranes were thought to have ruptured prematurely was included. There were no nonoamniotic multiple pregnancies.

Table II compares the study series to all deliveries. It will be noted, as in previously cited studies, that parity, fetal sex, the incidence of cesarean section, intrapartum and

Table I. Incidence of spontaneous premature rupture of membranes*

Spontaneous rupture of membranes			
(over 500 grams)	2,887	1:15.7	6.4%
Over 2,500 grams	2,367	1:18.8	5.3%
501 to 2,500 grams	515	1:86.8	1.1%

^{*}Total deliveries, 44,723.

Table II. Complications in study series and all deliveries

	over 3	All infants over 500 grams (44,723)		ntaneous ure series 1-2,500 rams (515)	
	No.	%	No.	90	
Primiparas	13,225	29.6	149	28.9	
Prolonged labor	285	0.6	4	0.8	
Cesarean section	2,554	5.7	32	6.2	
Hemorrhage	1,891	4.2	28	5.4	
All toxemias	1,963	4.4	18	3.5	
Specific toxemias	1,665	3.7	11	2.2	
Males	22,741	50.8	242	47.0	

Table III. Mortality and complications in study series and all deliveries

	All infants over 500 grams (44,723)		Spontaneous rupture seri 501-2,500 grams (515)	
	No.	%	No.	%
Perinatal mortality	1,126	2.5	159	30.9
Maternal morbidity	825	1.8	40	7.8
Breech presenta-				
tion	1,724	3.8	109	27.6
Abruptio placenta	912	2.0	38	7.4
Circumvallate				
placenta	600	1.3	30	5.8
Multiple pregnancy	498	1.1	40	7.8

postpartum hemorrhage, all toxemias, and pre-eclampsia-eclampsia are not significantly different in the compared groups. The average length of labor was shorter when compared with that of similar patients without premature rupture, but there is no significant difference in the incidence of prolonged labor. It is a little surprising that there were 4 patients who had labors of over 36 hours

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in spite of the accelerating influence of premature rupture and the small size of these infants.

The factors which seem significantly increased in the study group compared to all deliveries are perinatal mortality, maternal morbidity, and breech presentation (Table III). It will also be noted from Table III that the associated pathology of abruptio placentae, circumvallate placenta, and multiple pregnancy show a definite increase in the study group. In light of the etiological factors discussed, these latter factors might be related to abnormal structure of the membranes or to a rapid increase in pressure on the membranes, or to both. No information was available on the incidence of vaginitis or cervicitis.

Perinatal mortality versus latent period

Perinatal mortality is unquestionably the most important problem associated with the premature rupture of the membranes. Table IV emphasizes the role of prematurity in the study series as compared to that in all premature infants delivered during the 10 years. The smaller the baby at birth the less chance it has of survival. However, since no one has demonstrated a reliable method to prevent the onset of labor after the membranes rupture and there is no proof that this would be wise in every event, other factors must be evaluated which might reduce the perinatal mortality when this problem is dealt with.

It is apparent that premature infants between 1,500 and 2,500 grams who are born after spontaneous premature rupture of the membranes fare somewhat less well (19.2 per cent mortality) than do all premature infant not associated with this accident (15.1 per cent mortality). When the subdivisions of prematurity by size are compared (Table V) this difference is greater the larger the premature infant. When one considers the formidable problems confronting the babies born prematurely not associated with premature rupture of the membranes (placenta previa, premature separation of the placenta in premature infants, toxemia resulting in premature infants, etc.), it seems that there must be factors about which something might be done to save more babies born prematurely because of unfortunate premature rupture of the membranes.

Other than prenatal treatment of vaginal and cervical infections, adequate nutrition and general health measures, no accepted suggestions have been made to try to prevent premature rupture of the membranes.

It is evident from Table VI that half of the patients with premature rupture will go into labor within 48 hours (the latent period), and Table VIII shows that those who go longer than 48 hours before the onset of labor have a seriously greater perinatal mortality especially in the larger premature infants that might otherwise be expected to live. Others8, 19 have shown that whenever the latent period exceeds 48 hours the perinatal mortality increases sharply. When the 2,362 term or near term babies (over 2,500 grams) are studied from this point of view it is found also that fetal loss is three and one-half times greater if labor does not start within 48 hours. This, therefore, points up the first factor in addition to

Table IV. Mortality in study series and in all premature infants

Perinatal mortality by weight	All prematures (2,186)			Rupture of membranes series (515)		series
(grams)	Total	Deaths	%	Total	Deaths	%
2,001-2,500	1,102	110	10.0	318	44	13.8
1,501-2,000	411	137	33.4	88	34	38.6
1,001-1,500	311	202	65.8	69	43	62.3
501-1,000	362	346	95.6	40	38	95.0
501-2,500	2,186	795	36.3	515	159	30.9

Table V. Mortality in study series and in prematures not associated with premature rapture of the membranes

	All prematures not associated with premature rupture of membranes (1,671)				series	
	Total	Deaths	%	Total	Deaths	%
2,001-2,500	784	66	8.4	318	44	13.8
1,501-2,000	323	103	31.9	88	34	38.6
1,001-1,500	242	159	65.7	69	43	62.3
501-1,000	322	308	95.7	40	38	95.0

prematurity which must be considered as a cause of infant loss, namely, a latent period of over 48 hours (time of rupture to onset of labor). Since half of the patients will not go into labor spontaneously before 48 hours, its significance is apparent.

Table VII shows that the larger the infant the better the chance that labor will start before 48 hours. However, if one again notes that for all premature infants over 1,500 grams in this series when labor did not start before 48 hours the perinatal mortality was more than twice (27.7 per cent) that where labor did begin by 48 hours (12.3 per cent) (Table IX). This would seem to question the often-made assumption that time in the uterus of over 48 hours after the rupture of the membranes is to the infant's advantage as far as survival is concerned.

Gestational age

Another yardstick by which one can judge the fetal hazards involved is the weeks of gestation at the time of rupture. Table X shows that in approximately one fourth of the patients the membranes ruptured at 30 weeks or less while one tenth were thought to be at or near term. Two thirds of the ruptures occurred between 31 and 38 weeks with a perinatal mortality of 20.4 per cent. Analysis of these groups by weight and latent period again confirmed the importance of fetal weight but when infants are over 1,500 grams or have a gestational age of over 30 weeks a latent period of over 48 hours reduces chances for fetal survival. The outlook for fetuses under 1,500 grams or less than 31 weeks' gestation is extremely unfavorable. The length of the latent period has little effect on this latter group.

Maternal morbidity

Table III shows maternal morbidity to be roughly four times as great in the premature rupture series as in the general experience in this hospital (7.8 per cent versus 1.8 per cent). All previous reports do not agree with this. Table XI also at first glance might lead one to believe that there was no increase in

Table VI. Latent period in spontaneous rupture of membranes

Latent period	No. infants	%
1-6 hours 6-12 hours 12-24 hours 24-48 hours	73 46 73 90 } 26	$ \begin{array}{c} 14.2 \\ 8.9 \\ 14.2 \\ 17.5 \end{array} $
48-72 hours 3-7 days 7-14 days Over 14 days	$ \begin{array}{c} 48 \\ 101 \\ 52 \\ 72 \end{array} $ $ \begin{array}{c} 25 \\ \hline 25 \end{array} $	$ \begin{array}{c} 9.3 \\ 19.5 \\ 10.1 \\ 14.0 \end{array} $ $ \begin{array}{c} 49.3 \\ 49.3 \end{array} $

Table VII. Spontaneous rupture of membranes

Weight	1 to 48	hours	Over 48 hours	
(grams)	Infants	%	Infants	~ %
2,001-2,500 (318)	197	62.0	121	38.0
1,501-2,000 (88)	32	36.4	88	63.6
1,001-1,500 (69)	23	33.4	46	66.7
501-1,000 (40)	9	22.5	31	77.5
501-2,500 (515)	261	50.7	254	49.3

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Table VIII. Perinatal mortality in relation to weight and latent period

Weight	1 to 48 hours		Over 4			er 48 hours
(grams)	Total infants	Deaths	%	Total infants	Deaths	%
2,001-2,500	197	19	9.6	121	25	20.6
1,501-2,000	32	10	31.2	56	24	42.8
1,001-1,500	23	14	60.8	46	29	63.1
501-1,000	9	5	55.6	31	31	100.0
501-2,500	261	48	18.8	254	112	44.1

Table IX. Perinatal mortality and latent period

	1 to 48 hours			(Over 48 hours	
	Total infants	Deaths	%	Total infants	Deaths	%
1,501-2,500	229	29	12.3	177	49	27.7
501-1,500	32	19	68.7	77	60	78.0

Table X. Perinatal mortality in relation to time of rupture of membranes

Weeks	Infants	Deaths	%
Under 30	117 (22.7%)	86	73.5
31-34	150 (29.1%)	35	23.3
35-38	183 (35.5%)	33	18.0
Over 38	55 (10.7%)	5	9.1
Total	515 (100.0%)	159	30.9

Table XI. Maternal morbidity in relation to latent period

	1 to 48 hours (261)		Over 48 hou (254)	
	Morbid	%	Morbid	%
Spontaneous rupture series 501-2,500 grams (515 patients)	19	7.3	21	8.3

maternal morbidity when the latent period exceeds 48 hours. Nearly all of the 142 patients receiving antimicrobial therapy were in the group with latent periods of over 48 hours. This may explain this equality in the morbidity of the two groups.

Maternal morbidity was the same in the 142 patients who received antimicrobial therapy as in the 373 who did not (Table XII). Since all patients with evidence of sepsis were given antimicrobial agents, this may speak well for the use of these agents in such cases.

Antimicrobial therapy

We often ask ourselves "should antimicrobial therapy be given to patients with spontaneous premature rupture of the membranes?" If so, which patients should receive it and what antimicrobial agents should be used and when should they be given? In this series of 515 patients there were 142 who received therapeutic doses of such agents with a perinatal loss of 40.8 per cent. In the 373 patients who did not receive this type of treatment the perinatal loss was 27.1 per cent (Table XIII). From this, one might conclude that such therapy not only did no good but actually increased fetal loss. In a study of the two groups, however, it is apparent that nearly all patients with amnionitis received such treatment and the infants were much smaller at birth. Without considering the evidence of amnionitis but correcting these figures for fetal birth weight alone, we find that only 29.4 per cent of babies of comparable size were lost when antimicrobial therapy was given and 37.6 per cent were lost if it were not given. The

Table XII. Maternal morbidity and antimicrobial treatment

	Patients	Morbid	%
Antimicrobial therapy	142	11	7.7
No antimicrobial therapy	373	29	7.8
Total	515	40	7.8
All deliveries	44,723	825	1.8

correction was accomplished by averaging the percentages of fetal loss of the four 500 gram increments of each group.

We may also note from Table XIII that there was no significant difference between giving the agents during labor only or before (during the latent period) and during labor. These two groups were comparable as to prepartum and intrapartum sepsis and fetal size at birth. The type of agent used in the 142 patients receiving therapy was as follows: 125 patients received penicillin, 72 received dihydrostreptomycin, 12 received sulfonamides, and 12 received one or more of the newer broad-spectrum antibiotics. No comparative analysis of the different agents can be made. Most patients received therapeutic doses of penicillin or penicillin and dihydrostreptomycin so any effect on the results is most likely due to these two agents.

It seems reasonable therefore that penicillin and dihydrostreptomycin therapy should be given to all patients with evidence of amnionitis and during labor in all patients whose membranes have been ruptured for more than 48 hours before the onset of labor. There is no evidence that such treatment is of value during the latent period unless evidence of sepsis is present.

Breech presentation

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It would be expected that an increased incidence of breech presentation might be

found in this group of premature labors. Table III shows that 109 or 27.6 per cent of these babies were in breech presentation and of these 103 were delivered vaginally. There were 376 vertex vaginal deliveries in this study. Table XIV shows comparative perinatal mortality rates of these two groups. . Why should the mortality be twice as much in breech vaginal deliveries as in similar vertex vaginal deliveries? The relatively small body compared to the large head in the premature may be the answer. All obstetricians have been trapped in this dilemma. The cervix of the patient in premature labor is also known by experience to be much less negotiable than when the patient is at term. This evidence suggests that the management of breech presentation in the premature infant should be given special consideration. If vaginal delivery of premature infants doubles the fetal loss the technique of vaginal delivery employed is unsatisfactory and perhaps abdominal delivery should be considered.

Other observations of interest were the role of cesarean section, the problem of prolapse of the cord, and the use of oxytocin in the induction of labor in this series of 515 premature infants.

There were 32 cesarean sections (6.2 per cent) of which 25 were low cervical, 2 were classical, and 5 were extraperitoneal. The indications are listed in Table XV. Obviously, some patients had more than one listed indi-

Table XIII. Perinatal mortality and antimicrobial treatment

Antimicrobial treatment		Infants	Deaths	%	Mortality
During labor only		48	19	39.6	Corrected for
Before and during labor		94	39	41.5	infant weigh
All antimicrobial treatment		142	58	40.8	29.4
No antimicrobial treatment	1	373	101	27.1	37.6

Table XIV. Spontaneous rupture of membranes versus all vaginal deliveries (479)

Weight	Breech (103)			Cephalic (376)		
(grams)	Infants	Deaths	%	Infants	Deaths	%
2,001-2,500	45	. 8	17.8	244	32	13.1
1,501-2,000	20	12	60.0	68	22	32.3
1,001-1,500	29	25	86.2	35	16	45.7
501-1,000	_9	8	89.0	29	29	100.0
501-2,500	103	53	51.4	376	. 99	26.3

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Table XV. Indications for cesarean section

Abruptio placentae	6
Placenta previa	5
Previous cesarean section	5
High social value of child	4
Cephalopelvic disproportion	3
Transverse presentation	2
Prolapse of the cord	2
Primary uterine inertia	2
Breech presentation	1
Previous stillbirths	1
Other	6

cation. Cesarean section was performed in the presence of breech presentation in 6 cases; however, in only 1 was the breech the indication for section. Two of the 5 babies presenting by the breech died. Of the 26 babies in vertex presentation delivered by cesarean section, 5 died. There was one maternal death and this patient was delivered by cesarean section.

Prolapse of the cord was diagnosed 16 times. Two of these babies were delivered by cesarean section and lived. Fourteen were delivered vaginally and, of these, one lived, 2 died in the neonatal period, and 11 were stillborn. None of the prolapsed cords occurred in the 40 multiple pregnancies in this series.

Induction of labor with oxytocin was attempted fifty times on 45 patients. All 45 responded, 4 of them after two or more attempts. Six of the 45 patients had breech presentations and 3 of these infants were lost. Of the 39 vertex presentations 16 babies were lost. No clear-cut indications were used for medical induction. The majority were done because no fetal heart tones could be heard or because there was evidence of amnionitis.

Summary and conclusions

- 1. A study of 515 consecutive patients sustaining this complication in which premature infants were delivered during a 10year period in a private general hospital is presented.
- 2. Three important considerations are pointed up by this study: (a) when the membranes are ruptured more than 48 hours before the onset of labor fetal loss is significantly increased; (b) the administration of penicillin and dihydrostreptomycin in patients with evidence of sepsis and during labor in patients whose membranes have been ruptured more than 48 hours has a favorable influence on perinatal mortality; (c) breech presentation with vaginal delivery in itself significantly increases fetal loss when spontaneous premature rupture of the membranes is sustained and the infant weighs under 2,500 grams.
- 3. Management should therefore include: (a) careful consideration of the advisability of allowing these patients to go more than 48 hours with ruptured membranes before induction or abdominal delivery; (b) improved techniques of delivery of these premature infants when they are in breech presentation; (c) antimicrobial therapy in all patients with evidence of amnionitis and during labor in all patients whose membranes have been ruptured for more than 48 hours.

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Discussion

Dr. Ralph L. Hoffman, San Diego, California. The facts that approximately 50 per cent of perinatal mortality is due to prematurity and that 10 to 20 per cent of prematurity results from the spontaneous premature rupture of the membranes emphasize the importance of this problem.

Etiological factors in individual cases are usually not known. In an occasional case the incompetent cervix or other structural abnormality correctible by operation may exist. In trying to ascertain the precipitating event, several years ago I questioned a number of my patients whose membranes had ruptured prematurely and was told by more than 60 per cent that the patient was turning over or had just turned over in bed when rupture occurred! Dr. Breese suggests that sudden pressure changes, such as would accompany this activity, cause the rupture.

Since receiving Dr. Breese's paper I have studied a much smaller series of similar cases at a San Diego Hospital. We did have better results following a longer latent period. In some cases with successful outcome there was drainage for 6 or 8 weeks, and in one of my recent cases there was profuse drainage for 17 weeks, terminating in the delivery of a normal baby at term. Those premature infants with latent periods of 2 to 7 days had the worst prognosis.

Efforts to prolong the latent period have been discouraging. Hormones seem worthless. Often the patient who will develop premature rupture of the membranes or go into labor shortly after its occurrence is nervous and hypertonic, and complains of cramps and pains; on examination she is observed to have increased tone and contractility of the uterus. I have used psychotherapy

and tranquilizers during pregnancy or after rupture of membranes in these women and it seems there has been some benefit. Dr. Purvis Martin has some similar ideas on this problem.

After premature rupture of the membranes I put the patient to bed but, in the absence of such complications as prolapse of the cord, abruptio placentae, etc., allow her up after 24 or 48 hours. She is urged to take extra amounts of fluid. The importance of avoiding contamination is pointed out. I have been appalled by the things patients with ruptured membranes do to themselves: douches, suppositories, etc. Unless there is obvious infection, antibiotics are not used until labor begins and then vigorous treatment, usually with broad spectrum antibiotics, is carried out throughout labor and following delivery. The situation should be discussed at once with the pediatrician so that he may treat the newborn infant promptly.

Vaginal delivery is probably better for the premature infant, and the nearer to term the patient the sooner we attempt to induce labor. In our series we performed more cesarean sections in the presence of premature breech presentations and our results were better, the figures being more nearly those given by Dr. Breese for equivalent cephalic presentations. Cesarean section with a premature infant will not always assure a living baby or an infant who will survive the neonatal period. There is nothing more disconcerting than doing a cesarean section and then having the baby die in the neonatal period. In the absence of other indications, I certainly would not urge the frequent use of cesarean section merely because the membranes have been ruptured more than 48 hours.

Usefulness of paracervical block in obstetrics

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PARACERVICAL block anesthesia has been used in gynecological procedures for many years but its usefulness in obstetrics has not been fully appreciated.

The first report of the use of paracervical block anesthesia in obstetrics was by Gellert1 of Germany who reported in 1926 a series of 30 cases in which he produced relief of first stage labor pains by injecting 10 c.c. of 1 per cent procaine into the parametrium on each side of the cervix. The following year, Pribram² of Germany reported a series of what he called blocking the uteropelvic plexus to remove the pains of labor. Henriet,3 also of Germany, reported 85 cases of blocking the pelvic-peritoneal plexus with good results. Rosenfeld4 of New York was the first American author to use paracervical block anesthesia in obstetrics, and he reported on his success in 100 cases. His article appeared in the American Journal of Obstetrics AND GYNECOLOGY in 1945. The next American proponent of this type of anesthesia was Freeman⁵ of Minnesota, who published his technique and results in Obstetrics and Gynecology in 1956.

In all the literature on paracervical block anesthesia in obstetrics, the authors have described a simple and safe method of relieving first stage labor pains, yet it is strange that so few obstetricians have attempted this procedure. We have been using this form of block anesthesia since 1956 and have found it to be very valuable.

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Pelvic neurophysiology

In order to understand the principle of paracervical block anesthesia, it would be well to review briefly the neuroanatomy of the uterus and the pathways of pain in labor.

The intrinsic cervical ganglia in the human have been studied by Gemmell,⁶ Reynolds,⁷ and Murphy.⁸ They consist of diffuse micro- and macroganglia scattered throughout the subserosal coat and uterine musculature of the cervix and lower uterine segment. The point of highest distribution of these structures is at the level of the internal os. They are especially concentrated around the uterine blood vessels.

Davis⁹ and Cleland¹⁰ have shown that the pain in the first stage of labor is due primarily to dilatation of the cervix and to a lesser extent to contractions of the body of the uterus. Pain impulses pass by sensory pathways in company with the sympathetic nerves traveling down the lateral and posterior portions of the cervix into the uterosacral ligaments. They pass through the uterine plexus, pelvic plexus, and hypogastric plexus into the lumbar and lower thoracid sympathetic chain and then on to the ramin of the eleventh and twelfth thoracic nerves to reach the spinal cord.

With this neuroanatomy in mind, relief of the first stage labor pains may be accomplished in the following ways: (1)

From the Alta Bates Community Hospital.

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. subarachnoid block (spinal); (2) lumbar spidural block; (3) caudal block; (4) lower shoracic and paravertebral block; (5) uterosacral block; (6) paracervical block.

Paracervical block is the simplest of all the methods, with the fewest complications. We are all aware of the potential complications of spinal and caudal anesthesia, even to the extreme of maternal death; however, there has yet to be reported a serious complication of paracervical block.

Paracervical block does not relieve second stage labor pains, for this is due to distention of the vagina and vulva and the pain pathways are via the pudendal nerve. These fibers enter the spinal cord via the posterior roots of the second, third, and fourth sacral nerves. The use of pudendal block in delivery is well known and widely used. A combination of paracervical and pudendal blocks make a simple and safe way to relieve the pain of childbirth.

Technique

The technique of paracervical block is relatively simple, especially if adequate needle guides* are available. A guide can be easily made by cutting a 4 inch piece of small polyethylene tubing to fit over a 5 inch, 21 gauge needle. The tubing protects the needle point while it is being guided into the lateral fornix. We maintain several paracervical block trays, sterile and ready to use (Fig. 1).

The patient is placed in the lithotomy position and prepared with pHisoHex and aqueous benzalkonium (Zephiran). A solution of dilute benzalkonium is used to irrigate the lateral fornices with use of an Asepto or bulb syringe. The uterovaginal fold is then located with the examining fingers and the needle is guided into the fold and inserted through the mucosa about halfway between the uterine artery and the uterosacral ligament. If the cervix were the face of a clock the sites of injections would be at 4 and 8

o'clock. Ten cubic centimeters of a 1 per cent solution of lidocaine (Xylocaine) is injected on each side for a distance of 2 cm. (Fig. 2).

The ideal time to do the block is when the cervix is 4 to 5 cm. dilated with the head at a 0 to plus-2 station. The block becomes more difficult when the cervix is more than 7 cm. dilated or the head closer to the perineum.

Lidocaine was used as the anesthetic solution in our series. Gray and Geddes12 in a review of over 100 local anesthetic agents state that lidocaine is one of the safest and most effective solutions. It is only slightly more toxic than procaine, yet has a much more rapid onset of anesthesia and a longer duration of action. Tetracaine (Pontocaine) and cinhocaine (Nupercaine) have both been tried in attempts to prolong the duration of the anesthesia but are considered too toxic to be used in the vascular parametrium. Epinephrine has also been used to prolong the anesthesia, but we feel this may cause dangerous vasoconstriction to the uterine blood supply and hence be a hazard to the fetus in utero.

Complications

In order to have paracervical block remain a safe anesthetic one must be aware of the potential complications and use adequate precautions. The theoretical maternal complications are: (1) puncture of a blood vessel with bleeding and hematoma formation, (2) infection, (3) intravenous administration, and (4) damage to the parametrial tissues and the structures they contain. The usual precautions exercised in any block anesthesia will prevent most of these potential maternal complications. The sites of injection at 4 and 8 o'clock were selected to avoid puncturing the uterine vessels.

Possible fetal complications are: (1) interference with the uterine blood supply with resultant hypoxia, and (2) puncturing the fetal presenting part with the needle point.

In about 20 per cent of paracervical blocks some degree of fetal bradycardia has

⁸Trumpet Pudendal Needle Guides, Iowa Medical Supply Co., Fort Dodge, Iowa; Kobak Transvaginal Regional Anesthesia Instrument, V. Mueller & Co., Chicago, Illinois.

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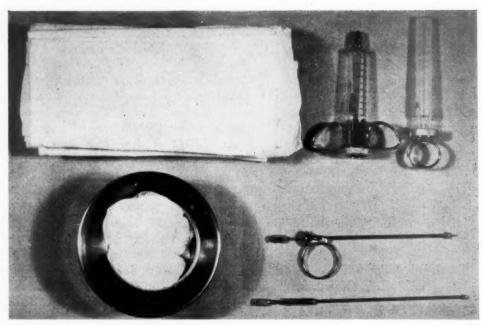


Fig. 1. Paracervical block tray.

been noted. Some are associated with maternal hypotension and are thought to be due to the "supine hypotensive syndrome." Turning the patient on her side in these cases will usually bring the fetal heart tones back to a normal rate. Other instances of bradycardia may be due to rapid absorption of the lidocaine in the fetal circulation with its depressing effect upon the myocardium. This bradycardia is transient and is rarely accompanied by any other signs of fetal distress.

Indications

The indications for paracervical block have not been clearly defined in the literature. The chief indication reported is the relief of pain in patients who fail to respond to the usual analgesics and become hysterical or difficult to manage. These patients usually become quiet and very thankful when paracervical block is instituted. The chief indication in our series is "cervical dystocia," frequently associated with left occipitoposterior positions. When the cervix remains at 4 to 5 cm. dilatation in spite of strong uterine contractions and becomes thicker and smaller rather than thinner and larger during contractions, there is a prime indication for

paracervical block. We think that the mechanism of this type of cervical dystocia in occipitoposterior positions is due to the direction of force in this presentation, exerting pressures on the uterosacral ligaments that contain the nerve supply, resulting in reflex spasm of the cervix. In these cases, paracervical block not only results in complete relief of pain but is usually followed by rapid cervical dilatation and delivery before the block has lost its effectiveness.

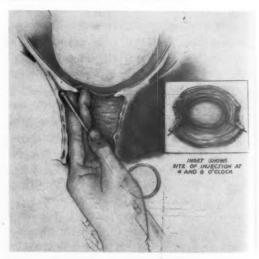


Fig. 2. Technique of paracervical block.

In cases where there seems to be no progress in dilatation in the absence of cephalopelvic disproportion, we find it advantageous to use paracervical block before considering a cesarean. There have been three consultation cases in our series where the attending physician had the operating room alerted for a cesarean section, but after paracervical block the patient made rapid progress and normal spontaneous delivery followed.

Paracervical block finds another of its most useful applications in providing relief of pain during curettage to complete a spontaneous abortion. Patients sometimes urgently require this procedure because of brisk bleeding and yet are unprepared for a general anesthetic because of a full stomach. In these cases paracervical block combined with a pudendal block has served our needs admirably.

We have also used a combined paracervical and pudendal block for the Shirodkar procedure to close the incompetent cervical os during pregnancy. The suture was placed without discomfort to the patient and with little premedication. This seems to be the safest anesthetic for this procedure.

In our series, 5 patients were selected for elective induction. They were multiparas with previous histories of precipitate labors who were found to have soft, thin, dilated cervices on office examination. These patients were admitted to the delivery room. A paracervical block was followed by stripping and rupturing of the membranes. A transvaginal pudendal block was then performed with a small amount of dilute oxytocinon (Syntocinon) added to the lidocaine solution. Four of the five patients were delivered spontaneously within the hour and without need for additional anesthesia. The ifth was delivered as the paracervical block was wearing off and she needed only whiffs of nitrous oxide for delivery.

Method of study

In order to collect data for this study, we performed over 100 paracervical blocks on patients in labor and kept detailed records. We noted the condition of the cervix one hour before the block, at the time of the

block, and one hour after the block. We also recorded the fetal heart tones before, during, and after the block.

The effectiveness of paracervical block in its relief of first stage labor pains is easily demonstrated. One side is blocked and the patient is then asked to describe her discomfort with the next contraction. Pain is felt only on the side not injected. The opposite side is then blocked and the patient is then unaware of any discomfort during a contraction. If she does feel some pain on one side or the other an additional 5 c.c. of lidocaine is injected on the side of discomfort.

Results

The number of patients who received partial or complete relief was almost 100 per cent. The use of sterile saline as a placebo instead of lidocaine to provide a control series was not attempted in this study done on private patients. The use of separate patients as controls is inherently difficult since the character of separate labors even in similar patients varies so widely. The rapid rate of cervical dilation after paracervical block therefore remains a clinical impression—but a very strong one.

The duration of anesthesia in our group, with use of the techniques previously described, was approximately 1 to 1½ hours. The shortest was only 45 minutes and the longest was 2½ hours.

There were no maternal complications. The only fetal effect was transient brady-cardia without other evidence of fetal distress in approximately 20 per cent of cases.

In a survey of 45 members of the Alameda-Contra Costa Gynecological Society, concerning their experience with paracervical block, there was reported one hematoma in the parametrium after blocking. This was the only complication we found in several hundred blocks reported in the survey.

Conclusion

Paracervical block is a simple, safe, and useful procedure with which those practicing obstetrics should be acquainted and which we should use when indicated.

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Discussion

Dr. L. Grant Baldwin, Pasadena, California. I am pleased to find that Dr. Page does not advocate this procedure as a routine one but reserves it for a specific need, namely, the patient with a fetus in the posterior position, with good contractions, but failing to progress. Some recent articles report its routine use. To my mind such a policy comes under the heading of meddlesome obstetrics or the use of a needless procedure. These same authors found that even when they had the will to use it routinely, 26 per cent of their patients were delivered too rapidly to permit the block.

I would like to commend the essayist's preference for doing these blocks in the delivery rooms. Others have advocated their administration in the labor bed. All obstetricians know that the slow, active labor with failure of progress associated with a posterior position of the fetus and its resultant backache tends to produce unruly patients. To attempt to inject the parametrium of these hyperactive and uncooperative women with sterile technique becomes impossible unless the lithotomy position is used.

Dr. Page widens his indications for this procedure when he uses it for anticipated precipitate labor in a multipara. If a low spinal had been given to these same 5 patients prior to the rupture of the membranes, the results would have been equally gratifying.

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I am favorably impressed with the report of trying the paracervical block before resorting to cesarean section in the patient in whom progress of labor has apparently come to a standstill.

Let us not, because of our enthusiasm for a procedure, become so overly eloquent in its praise that we convert generalities into specific statements that will not withstand careful scrutiny. Dr. Page stated, "We are all aware of the complications of spinal and caudal anesthesia, even to maternal death; however, there has yet to be reported a serious complication of paracervical block." However, he mentions 20 per cent with bradycardia and one reported case of hematoma. In addition, Freeman reports one fetal death following bradycardia with no adequate explanation, one severe maternal reaction to hexylcaine (Cyclaine) with a peripheral vascular collapse that persisted for an hour, and a child that died in 24 hours from pneumonia, possibly infected by a contaminated respirator. In addition, in the search for a longer lasting agent, a mixture of Efocaine and procaine was used in one case resulting in neuritis in the patient's left lumbar plexus with persistence of symptoms for 3 months.

In spite of these facts, this procedure seems to be a useful one in selected cases in the hands of the intelligent when used in an obstetrical department that is well equipped to cope with unexpected reactions.

Symposium on endometrial cancer

Introduction

JAMES F. NOLAN, M.D.

Los Angeles, California

THIS symposium on adenocarcinoma of the uterine corpus represents something of a new departure from the usual method of discussion of medical problems. It was suggested by President George Judd about a year ago and is an attempt to "sound out" the combined experiences of the memberbership and guests of the Pacific Coast Obstetrical and Gynecological Society on a single subject. In essence, it is designed to be a "group-think session" for the purpose of exchanging ideas among the membership. Dr. Judd felt that the knowledge and experience of this entire group represented a source of untapped information which could be utilized by ourselves as well as others.

The importance of the subject to be discussed does not lie only in the direct influence it bears upon the lives of patients harboring adenocarcinoma of the uterine corpus who may come under the care of physicians. It is also important from a more generalized viewpoint in relation to the physiology of reproduction in the female. Such questions of possible increasing incidence in terms of population increase and increased age span, the questions of etiology and possible prevention of the disease,

the questions of diagnostic methods and their improvement, as well as the questions of preferred methods of management, all tend to make the subject of wide interest among specialists in the field of obstetrics and gynecology.

The method of presentation is again somewhat different in that it is based on collected statistics rather than upon smaller individual experiences. It is hoped that this direction toward the "big picture" of the disease will give the discussion a wider scope and perhaps a more useful interpretative view of the problem.

Certain data have been furnished us by Dr. Lester Breslow, Chief of the Bureau of Chronic Diseases of the State of California Department of Public Health. The data have been collected by the California Tumor Registry and represent a tremendous effort upon the part of Dr. Breslow and his staff. Of course, in a certain sense, the value of such a collection of statistics can be culminated only by its use and interpretation. So, realizing our responsibility as physicians charged with patient management, we hasten to recognize our indebtedness to Dr. Breslow and his staff. We wish to thank him for the opportunity of presenting these data in this manner.

These data include the collection of reported cases of cancer of the uterus which, under the International Classification Sys-

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960.

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tem (WHO), include three categories. These are diagnoses of: (172) malignant neoplasm of corpus uteri; (173) malignant neoplasm of other parts of uterus, including chorion-epithelioma; (174) malignant neoplasm of uterus, unspecified. The diagnosis of "malignant neoplasm of cervix uteri" is excluded.

The bulk of the data, then, refers to carcinoma of the endometrium, although the methods of reporting and collection cannot exclude the rarer neoplasms of the uterine corpus.

All of the members of the Society and guests have been provided with the same data along with the covering explanation of the methods of collection and uncertainties in it. No further attempt will be made to present the statistics as a whole but, rather, assigned discussants from the membership and guests will give introductory remarks on various phases of the problem in relation to the data from their own experience. It is hoped that the discussion may then become general among the auditors so that it will represent the voice of the entire assembly.

In advance, I should like to thank the assigned discussants as well as those who wish to speak from the floor later in the session. I appreciate that this is an innovation and that it represents "togetherness" in its basic sense. However, I hope that it will be fruitful to all of us.

Incidence

ARTHUR B. NASH

Victoria, British Columbia

ALTHOUGH reference to many authors' work fails to reveal acceptable proof that the incidence of endometrial cancer is showing an absolute increase, such would nevertheless appear to be the case from the available evidence. At least such is true with respect to the *reported* cases as revealed from multiple sources.

In Canada, unfortunately, there is a discouraging lack of accurate information available as to the incidence of endometrial carcinoma in that uterine cancer is often reported without distinction between corpus and cervix.

It is likewise difficult to establish with certainty that endometrial carcinoma has shown, or is showing, a tendency to relative increase in relation to the incidence of cervical carcinoma. Yet one can recall a relative incidence a few years ago, as quoted in the literature, of 11 or 12 to 1. The present-day relative incidence, varying as it does from equality to perhaps as high as 7 to 1, with an average reported relative incidence of about 3 to 2, gives a strong indication that the disease is increasing in incidence as compared to cervical carcinoma. Since endometrial carcinoma is essentially a disease of later life, it may be that, over the years, an increase in life expectancy has in some degree contributed to this changing trend. Cosbie and associates1 have stated that in their experience carcinoma of the corpus occurs 11 years later than carcinoma of the cervix. The average age in cases at the British Columbia Cancer Institute cases has been 62 years; this is 9 years later than for cervical carcinoma.

In the collective view of most authors the especially predisposed individual is in the

attention to the more satisfactory and more accurate diagnosis of cervical carcinoma by this means. Certain it is that the former is more difficult and less accurate, but it is questionable whether its possibilities have been exploited to the fullest. One cannot help but feel that we have not been sufficiently aggressive in the early diagnosis of this disease.

Javert³ has said that in endometrial carcinoma "it may already be too late when clinical symptoms have developed" and he emphasizes that the key to early detection lies in the routine use of cytology, endometrial biopsy, and curettage in asymptomatic menopausal and postmenopausal women.

One cannot escape the hope that the current study undertaken by Miller⁴ at the University of Michigan, in which every patient admitted for curettage receives a vaginal cytology smear, an endometrial suction lavage, an endometrial suction biopsy, and a fractional curettage, may yield encouraging results leading to the exploitation of any or all of these techniques in attaining the goal of early diagnosis.

For the time being particularly, it is my feeling that, until this evaluation is complete or until better methods are devised, we should all entertain a high index of suspicion and develop an aggressive approach to the crucial problem of early diagnosis before the development of symptoms, especially in those individuals whom we can readily identify as being susceptible or predisposed to a higher incidence of this disease than the general population.

age period of from 50 to 69 years and she may well have a family history of corporeal cencer. She is probably nulliparous or has at least experienced a degree of infertility. Physically, she is inclined to be large and in at least half the cases there is some degree of obesity. If she has ceased to menstruate, the menopause will have been delayed until after the age of 50 and will frequently have been preceded by hypermenorrhea, and she may have exhibited demonstrable endometrial hyperplasia at some preceding time. She is probably hypertensive and, if she does not have overt diabetes, some degree of disturbed sugar metabolism may be manifested by an abnormal surgar curve. Her uterus, moreover, will harbor fibroids in an appreciable proportion of cases and the presence of associated endometrial polypi has an incidence of about 33 per cent, according to Stanley Way,2 who emphasizes his opinion to the effect that a postmenopausal uterus containing a polyp, especially if the menopause has occurred past the age of 50 and if the patient is a diabetic, is a menace and should be removed.

Here then, we see an individual who, by reason of her possession of some or all of the characteristics just enumerated, is predisposed to the development of endometrial carcinoma. In her, and those like her, the incidence of this disease is relatively high. With this knowledge it is not unreasonable to suggest that these patients should not be merely recognized but that they should be aggressively sought out, and that a determined endeavor be made in such a patient, predisposed as she is, to screen her with meticulous care so that at least she, if not all women with endometrial carcinoma, may have the benefit of early diagnosis. Early diagnosis and good prognosis are handmaidens in this often lethal disease. Let us then select, if select we must, those women whom we recognize as predisposed, for the most careful observations.

In my view, the difficulties involved in and the limitations of cytological diagnosis of endometrial carcinoma have been exaggerated by those who choose to confine their

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Problems in diagnosis of cancer of the endometrium

HERBERT F. TRAUT, M.D.

San Francisco, California

THERE is no clinical symptom pattern that can be said to be indicative of endometrial cancer. Of those most usually considered is post menopausal bleeding, and yet how frequently do we see postmenopausal bleeding due to malignant disease? Usually it is due to atrophic vaginal epithelium, cervical or endometrial polyps, or, more often than any other cause, estrogenic therapy. The latter is a very substantial "red herring" drawn across the clinician's trail. However, when the therapy of estrogens can be eliminated or evaluated there is still the explanation of postmenopausal bleeding, intermenstrual spotting, or actual bleeding.

Having been raised in the school of cytological screening I depend on the reading of vaginal smear spreads. Most cases of paramenopausal spotting, or those of frankly postmenopausal incidences, have other than malignant connotations. Most often it is due to endocrine factors, either pre- or postmenopausal, often complicated by estrogen therapy. On the other hand, there is the thinning out of vaginal epithelium of the menopausal patient subject to the trauma of coitus or the accidents of vaginal douching.

Occasionally there is a vaginal smear report which reveals atypical cells with dysplasia as to the nucleus and cytoplasm. These indices, when observed and evaluated by an experienced cytologist, are significant and should have thorough investigation. Cytological diagnosis of endometrial cells is admittedly more difficult than diagnosis of squamous cells. They are often clumped and stain poorly because they are shed after a substantial degree of pyknosis has occurred. In our hands we can achieve an 80 per cent degree of accurate diagnosis, but this cannot be attained by many laboratories;

hence the reliance upon endometrial biopsy.

Endometrial biopsy as an office practice has varied degrees of reliability. The experienced physician with suction curette may be able to obtain tissues which indicate cancer of the endometrium. However, in any hands, such a procedure, regardless of how experienced the physician may be or how admirable and reliable the pathological laboratories may be, is not definitive where the diagnosis is negative. When positive, such practice is timesaving and rewarding. It cannot be depended upon. If repeated cytological examinations reveal atypical cells with nuclear dysplasia, the patient deserves a thorough curettage under anesthesia. There is no short cut, at this time, available to the physician under these circumstances. Curettage should be conducted in such a manner that a specimen may be available from the endocervix and biopsies from the various surfaces of the fundus may be differentiated in the pathological laboratory.

Admittedly the clinical evaluation of the character and extent of endometrial carcinoma is difficult and frequently incorrect. However, the above-discussed steps and considerations are helpful and yield us the most reliable information upon which to base our plans for therapy. Rarely can one delete any one of the steps toward evaluation. There are many of us who may feel that cytological study is unreliable or misleading. On the other hand, curettage in the office, and especially curettage without differential biopsy, may also be unreliable. A combination of both procedures gives one a rewarding reliability. This, with an experienced evaluation of the extent and location of the lesions and their morphological character, is the basis for the best treatment. Ŋ.,

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Histology in relation to carcinogenesis

RICHARD L. TAW

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THE title of this presentation automatically places me in the position of discussing a subject that is of waning interest. Today the emphasis is on intracellular mechanisms. The normal and pathological histological patterns have been reasonably well established during the past century in so far as they can be with available instruments. However, there is some excuse for taking your time with this subject if we approach it by using some of the current thinking about carcinoma.

As introduction I would like to remind you that the modern definition of carcinoma is purely cellular. Twenty years ago invasion had to be demonstrated before a process could be called carcinomatous. Now we accept certain cellular abnormalities as proof enough. This point is particularly important in the area under discussion today because, except for the most anaplastic types, adenocarcinoma retains the basement membrane, and it is groups of cells that form the invasive unit, not single cells.

Whatever the definition, our basic method of diagnosis has not changed. Long ago it was recognized that certain cellular appearances and patterns when viewed through the microscope represented carcinoma. Through the years our thinking and instruments have been refined, but it is still histological diagnosis in the last analysis. Since we have been limited to various methods of visual demonstration, the scope of our thinking has been restricted. An excellent example is the difficulty encountered in getting us to expand our field of vision and recognize that the changes that we see through the microscope may be due to changes primarily in the host and only secondarily in the so-called cancer cells.

Whether or not carcinoma is an entity has been questioned. Most of the laboratory investigators believe that it is a process that may have several backgrounds. We, as clinicians, have not been too disturbed by this problem, because, entity or not, most of these things conduct themselves in an unpleasantly familiar pattern.

Recently the role of the host in etiology has been receiving increasing attention and is now accepted as real, however poorly defined. The role in containment is not a new thought. Mechanical barriers have been understood for some time. The demonstration that special cells, such as lymphocytes, may be cancerocidal in special situations has been clearly demonstrated, and the immunological aspects have been and still are receiving much study. Various methods of judging host response have been tried, but, so far, none have been found that are completely acceptable. The most recent, and one of the most interesting, was the attempt to use the buccal mucosal cells as a method of measuring radiation sensitivity. The inverse relationship between stage of disease and response in the mouth must represent differences in basic host resistance.

As elsewhere, different cell types are recognized in carcinoma of the uterus. Most of our attention has been focused on the epithelial cell which exhibits varying degrees of dedifferentiation without evidence of secretory activity. However, other forms of this epithelial cell do exist; for example, the occasional clear cell type, or metaplasia to the squamous cell with or without microscopic evidence of malignancy. The important point is that this epithelial cell exhibits malignancy in several physical forms. With this, it is interesting that the stroma appears

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so benign and does such an excellent job of sustaining its delinquent brothers who are doing their utmost to destroy it.

Stromal malignancies are just as variable as the epithelial in cellular appearance—round, spindle, giant, myxomatous, and mixed. Some even include epithelial elements. Again, several physical forms of malignancy in the same tissue.

Another histological and philosophical peculiarity of this disease is that the recognizable origin may be in a single small area, multiple areas, or diffused throughout the entire tissue.

If these histological differences represent true difference in cancer, inconsistancies are found that present theories of carcinogenesis are unable to explain. Perhaps the basic difficulty is the microscope—we have asked more from it than it is able to give.

It is interesting that, except for the cervix, cancer of the genitals and breast occurs most often in a senescent organ. These tissues are no longer functional in the age groups when carcinoma most often occurs. Basically, this means that the substances responsible for growth, in the sense that continued growth is necessary for repair and replacement during functional years, are no longer present in very great quantities. This subject has received much attention in our literature from the standpoint that these growth substances have persisted or have been present in abnormal amounts or fashion in the past life of the individual.

Thus, estrogen is being considered seriously as a carcinogen. It has been judged guilty principally by association. Evidence has accumulated of previous estrogen disturbances and concurrent hormonal difficulties in other systems. The microscopic evidence for continued estrogen activity in postmenopausal carcinomas is not universally accepted. If we lump all endometrial carcinomas together, estrogen as a trophic hormone, or as a chemical initiator or promoter, or as both no more explains all the vagaries than does any other theory. In some endometrial carcinomas estrogen may be the major factor in induction. However, the evidence available is far from unequivocal.

Probably the most pertinent question is whether these several types are the same disease or not. Carcinoma in a young menstruating woman in whom the endometrium sloughs each cycle seems far different from that in the postmenopausal woman. Sarcomas generally conduct themselves somewhat differently than do the epithelial tumors. Perhaps the differences that are visualized through the microscope are not real. All are surrounded by that unmeasurable factor—the host.

Nothing new has been presented here and I realize that the title subject has been treated rather freely. Much of this is controversial—and speculative—which usually creates more discussion than those areas that are clearly defined.

Treatment

CHARLES E. McLENNAN, M.D.

Palo Alto, California

TO SPEAK of treating endometrial carcinoma is to revive the smoldering argument over the virtues of preoperative use of intra-

uterine radium, as well as lesser arguments about preoperative x-ray therapy and prophylactic postoperative irradiation of the

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vaginal vault or of the entire pelvis. Two years ago, in a paper read before this Socety, I reviewed the historical development of the thesis that preoperative radium therapy was valuable and pointed out the lack of irrefutable evidence that this was so. Since that time the protogonists of preoperative radium have not produced any new and wholly convincing evidence of the validity of their opinion. Today one may still offer a sizable array of theoretical objections to preoperative radium-in particular, the very limited physical area through which a cancerocidal dose of radiation is delivered from a central radium source, the need for special apparatus and unusual skill to achieve a so-called proper application, the additional loss of time prior to removal of the lesion (and thus more time for metastases to be established), and the increased financial outlay.

Yet, as recently as August, 1960, Gusberg¹ stated again that peroperative radium will (1) devitalize the tumor and prevent implantation metastases, (2) diminish uterine size, thus making operation easier, (3) promote fibrosis, seal lymphatics, and prevent rupture of the uterus during operation, and (4) improve the cure rate. As evidence of improved cure rate when radium is used, he cites 124 cases of Stage II disease—that is, uteri up to size of a 21/2 months' pregnancy—with a cure rate of 71 per cent after operation alone, but 80 per cent after radium and operation. When the chi-square test of significance is applied to this particular group of Gusberg's values, one discovers that chance alone could produce the apparent difference in cure rate, or a greater one, in about 40 per cent of such comparisons. Or to put it another way, if there were really no difference at all in the results of the two modes of treatment we should find this apparent 9 per cent difference in cure ra es in about 40 per cent of samples of this size. This sort of information makes one seriously question the validity of the author's conclusion, namely, that Stage II endometrial cancer is benefited by preoperative radium application.

Table I. Treatment in cases of endometrial cancer reported to the Tumor Registry (1942-1956)

Type of treatment	No.	Per cent of total number	total
Operation	1,376	39	2/5
Operation and radia-			
tion	750	21	1/5
Radiation	949	26	1/4
Other or none	491	14	1/7

Table II. Five-year survival rates for patients with endometrial cancer (1942-1956)

	Per cent	Per cent surviving with			
Type of treatment	surviving all patients treated	Dis- ease local- ized	Re- gional spread	Remote metas- tases	
Operation Operation	71	81	57	26	
and radia- tion Radiation	70 47	83 61	49 33	31 9	

I hasten to add, however, that when one examines Gusberg's over-all results for 291 patients in various stages (121 treated surgically and 170 given combined therapy) the story appears to be different. In this instance the chi-square value suggests that there is a real difference in the two groups. This is not to say, however, that the results differ solely because radium was employed in one series and not in the other, since it is obvious that he had not set up a controlled experiment involving random selection-nor even alternate selection of patients. Thus, other variables almost certainly were introduced, particularly in view of the fact that the therapeutic preference in Gusberg's clinic was for preoperative radium placement. One might venture to guess that a preponderance of favorable patients were afforded this favored method of treatment. Statistics of this kind cannot resolve the basic issue of whether or not radium is worth using in endometrial cancer.

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That portion of the data available to us from the California Tumor Registry bearing on the question of treatment shows (Table I) that approximately two fifths of the patients in this large sample were treated by operation alone, and only one fifth by combinations of operation and radiation. This is not exactly what I would have predicted, considering medical school dicta over the past quarter century, and I suspect this may reflect the fact that in California surgery is a flourishing specialty while radium applicators are relatively scare.

The results achieved in the California sample are shown in terms of 5 year survivors in Table II. For all patients treated surgically the survival rate was 71 per central and for patients receiving combined therapit was 70 per cent—obviously not different but only 47 per cent of those who received only irradiation lived 5 years or more. Approximately 60 per cent of all patients lived at least 5 years after discovery. No real advantage for combined therapy can be shown from these data, irrespective of the extent of the disease at the time of treatment.

REFERENCE

 Gusberg, S. B.: Am. J. Obst. & Gynec. 83: 374, 1960.

Continuing evaluation

AXEL N. ARNESON, M.D.*

St. Louis, Missouri

IN DISCUSSING the statistical material at hand we might here digress to direct attention to the assessment of results in terms of the percentage survival of patients free of disease after a specified period of observation. Statements of that order present relative "cure" rates, but deal in only a broad manner with the various factors that affect survival. They represent the incidence of cancer control among the traced patients in a particular series who also have longevity equaling the period of time in question. Relative values may indicate adequately the effect of treatment for those patients, but are not comparable with the results obtained in other series due to the wide variation in factors that affect curability, longevity, and follow-up observations.

The curability of cancer varies in accord-

ance with the treatment procedure, but it is also dependent upon the killing potential of the tumor which is largely a factor of spread. The ability for growth by direct extension or by dispersion varies for tumors originating in different tissues as well as for the different stages of clinical advance in cancers of the same general type. If the rate of death from cancer is significantly different in two series of patients there must be either a difference in the effectiveness of treatment or a difference in curability. The rate of dying from cancer thus becomes important in assessing end results. Those data are not obtained from values given only in relative rates.

In dealing with patient survival over in extended time, cancer statistics are a so affected by death from causes other than the disease itself. The potential for longev ty can have a significant effect upon end e-

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lts. Follow-up experience will reveal a eater loss from intercurrent disease if the s ries includes a disproportionately high i cidence of patients of advanced age or with physical impairment. The rate of death from causes other than cancer are not given in relative results.

The assessment of results in cancer is aimed at weighing the effect of different methods of treatment upon comparable types of clinical material. Because of the variable factors that affect prognosis and longevity it is essential that statistical results include a statement upon the method of classification into different stages of clinical advance and the age and physical condition of patients. Those data are not included in tables showing the relative percentage survival of patients at different periods of observation. A more effective presentation can be made, however, by the use of accumulative survival per cent tables. Those tables show the accumulative rate of death from cancer and from intercurrent disease and the accumulated rate of loss to follow-up from unknown causes. The natural course of the disease is more clearly indicated, and the time within which cancer deaths occur is shown. A patient lost to follow-up during that period is more apt to die from cancer than one lost at a later date. Finally, the tables deal only with the patients at risk for the period of observation in question. Since the accumulative survival per cent is the product of the relative value for the unit of time in question and the immediately preceding period, the results of the early periods of observation are weighed upon all subsequent time intervals. An accumulative table can, therefore, include patients treated during the past year and weigh that result upon the stated value for 3, 5, 10, or any other number of years that some patients may have been observed.

Accumulative tables have been computed for 113 patients with corporeal cancer folloved after treatment for periods of 1 to 10 years. Clinical staging is in accordance with the International Classification. Patients with operable lesions who are physi-

cally suited to surgical treatment are classed as "clinically operable." That category is Stage I₁. Similar patients not suited to operation because of an associated constitutional disorder are termed "technically operable" and classed as Stage I2. Those two groups should be of comparable stages of tumor advance and differ only in physical status. The assessment of tumor "operability" is determined by clinical examination at the time diagnosis is established. Corporeal cancers believed too advanced for surgical treatment are classed as "inoperable" and designated as Stage II. "Corpus et collum" and "corpus et ovary" cases are deleted from the comparison here made.

Accumulative per cent tables and relative per cent tables for Stage I1 are not found to be significantly different. A high percentage of patients in that group survive 5 to 10 years. In Stage I2, however, the 5 year accumulative value is only 53.2 per cent, but the relative value is 60 per cent. The lesser value for the accumulative rate is due to the weight of unfavorable results in more recently treated patients. It may be due to less effective treatment or to errors in clinical staging that included more advanced forms, or it may be due to factors affecting longevity unfavorably, such as more advanced age of patients or a disproportionate incidence of associated constitutional disorders. No attempt is here made to search out those points of explanation. The immediate aim is to demonstrate the usefulness of accumulative tables. Adverse effects upon longevity are revealed in the accumulative rates for intercurrent disease. The 5 year value for Stage I₁ is 18.5 per cent and for Stage I2 is 23.4 per cent. The higher rate for the "technically operable" group is expected on the basis of unsuitability for surgical treatment. Accumulative tables prepared for different time intervals would reveal any disproportionate incidence of attrition due to intercurrent disease in the more recently treated patients in Stage I₂.

A more significant point is found in comparing the accumulative per cent deaths from cancer. The 5 year value in Stage I₁

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is 9.6 per cent, and in Stage I₂ it is 15.8 per cent. That difference would indicate that the "clinically operable" patients were more curable, but presumably the two groups represent comparable stages of advance. The difference must, therefore, be due to treatment, and it is reasonable to attribute that to the use of surgery in Stage I₁. There are indications believed important for the use of preoperative irradiation in those patients but that is a point of discussion beyond the scope of this presentation.

It is of interest to compare corporeal and cervical cancer. Death from intercurrent disease is much lower in the cervical group because they are younger individuals. The 5 year death rate from cancer is 13.2 per cent in Stage I and 39.0 per cent in Stage II. It is thus apparent the corporeal cancer is more "curable" than is cervical cancer,

but there is little difference in survival rate due to the greater loss by intercurrent disease in the corporeal group.

Accumulative tables present statistical data more realistically than do relative result values. They are important in that the more clearly indicate the various factors that affect survival in a particular series of patients. It has not been possible to compare the results from surgery with those from radiation with assurance that the comparison is made upon a uniform type of clinical material. Accumulative tables do not assure that such a study can be accomplished, but with changes in methods of treatment the accumulative tables will more rapidly assess any improvement in clinical results by utilizing the weight of more recently treated patients on long-term values.

Discussion

DR. LUDWIG A. EMGE, San Francisco, California. Dr. Nolan has pointed to the numerical increase of corpus cancer in California based on the figures presented by the Tumor Registry. I sincerely doubt that this indicates an increase in the actual cancer incidence but rather represents the result of the steady influx of older persons into California and the equally steady rise in the longevity of women. Since most of these newcomers are in the later decades of life when corpus cancer is the prevailing cancer in women, it is to be expected that the rate for this cancer will continue to increase, although death attributable to this cancer definitely is on the decline.

Dr. Nash, who also emphasized the importance of the age factor, referred to the still obscure relation of obesity and diabetes to corpus cancer. While all of us recognize the relative frequency of these metabolic disturbances, their etiological relation to cancer has remained obscure. Various studies have not brought forth evidence that any one particular hormone might be at fault. More important is the recognition that the existence of severe metabolic disturbances definitely lowers the chance for survival because they hamper radical therapy, especially operative procedures. As Dr. Taw pointed out, the capacity of a cancer cell to respond to ir-

radiation is an individual factor and not readily determined by cytological studies. However, as Dr. Traut pointed out, the cellular estrogen response of vaginal and endometrial cells is of some help in this respect and has proved itself to be so in my experience.

Each of the first three essayists has emphasized the importance of endobiopsy in regard to the initial diagnosis as well as in determining radiation response. In my experience it has been the most important tool in making an early diagnosis and is far superior to, cellular smear studies which, at best, are only 80 per cent reliable. Suction biopsy is gentle and therefore advantageous over curettage, which is prone to invite lymphatic and vascular dissemination of cancer cells.

I fully agree with Dr. Traut that the recognition of invasive stromal hyperplasia of the basal endometrium is an important indication that myometrial as well as lymphatic invasion is underway. It is for this reason that I resort to radical hysterectomy and lymphadenectomy in order to forestall overlooking this possibility. On the basis of my own material, I consider this situation to exist in from 5 to 10 per cent of patients operated upon by me.

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merine bleeding obscures rather than reveals the presence of cancer, but with the help of endo-Hopsy this fact can be readily obviated. In the Lie climacteric and postmenopausal patient bleeding may be a late symptom but it is commonly preceded by mucoid uterine discharge and a distinct softening of the cervix with a patent cervical canal. When this state is recognized the introduction of a uterine sound (Clark's test) is of further diagnostic value because if followed by a bloody show it hints at the existence of endometrial pathology calling immediate endometrial biopsy. Another point to observe is the state of the vaginal cells in regard to estrogen retention, According to the degree determined, either by the Papanicolaou technique or by means of Schorr's stain, the growth activity of endometrial cancer can be predicted. Naturally, the degree of differentiation of the malignant components again modifies conclusions so reached. These are simple hints which any competent physician can master readily.

Dr. McLennan and Dr. Arneson have expounded their ideas about choice of therapy. Dr. McLennan favors operation over irradiation or over the combination of the two. He pointed out that unnecessary manipulation of any kind should be avoided in order to minimize the spread of cancer cells, a principle which applies to cancer regardless of its location. It is for the same reason that I again warn against vigorous curettage.

Dr. Arneson discussed, among other interesting aspects of today's problem, the difference between clinical and technical operability. Both can be determined within limits but mistakes can be made in either direction. The trouble with today's emphasis on heroic operations is that the value of life receives little consideration and I sincerely question that, with very few exceptions, the chance for survival and the elimination of pain is bettered. I fully agree with Dr. Arneson that the selection of therapy must be individualized. I cannot believe, on the basis of many years of experience, that there is just one and only one way of treating corpus cancer.

To illustrate my reaction to the choice of therapy I present a brief account of 120 instances of endometrial cancer treated by me over a period of 20 years ending in 1954. This group actually consisted of 124 patients. Four of these were lost to follow-up after 5 years had passed and therefore are not included in this survey. The results in terms of method of treatment and survival in years are listed in Table I.

Death resulting from the original cancer was exceedingly rare in the first two groups but definitely more frequent in the third and fourth groups. The 5 years' survival was highest in the first group treated surgically, and radically so in the last 15 years, in order to learn more about lymphatic transmission of endometrial cancer. After a 10 years' survival period the figures for the prolongation of life approach each other, indicating that once 10 years have passed after therapy a latent recurrence of endometrial cancer is practically unknown. The next two groups, being less favorable in regard to ultimate survival, show a high percentage of death under 5 years. The over-all 5 year survival rate of 78.3 per cent for this series is well above the averages reported in the literature.

The method of therapy chosen for these various groups was based on the following factors:

Group I. Patients should be past the menopause with a highly differentiated cancer, as determined by endobiopsy, and a low estrogen retention, as determined by conventional cytologic methods. The uterus must be freely movable and not unusually enlarged, without palpable evidence of dissemination. The patient's physical condition should be good.

Group II. Commonly, this group includes patients in the premenopausal and early menopausal years on whom an active estrogen metabolism can be demonstrated. Cancer is multifocal and poorly differentiated, indicative of active growth. Contour changes of the uterus hint at invasion and mobility may be limited. These patients do better when adequately treated by radiation 4 to 6 weeks before operation, which should be radical to obtain information about invasion of the lymphatic system.

Group III. These patients were selected as stated under Group I but operative findings and subsequent pathological confirmation proved that the disease had spread beyond the original calculation. The surgical procedure was therefore supplemented by x-ray therapy in addition to radical operation as indicated at the time of pelvic exploration. This demonstrates the human error which upsets the best of calculations.

Group IV. By virtue of physical handicaps including cardiovascular, hormonal, and metabolic conditions, these patients were treated with irradiation, including radium and deep x-ray therapy.

Group V. These patients were not treated because of the advanced state of the cancer. According to statistics obtained from the California

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Table I. Survival study of 120 private patients treated for endometrial cancer in 20 years

Тһетару		Died under 5 years		Survival in years							
				5+		6-10		11-15		16-20+	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Operation	58	2	3.4	56	96.6	49	84.5	22	37.9	16	27.6
Radium and operation	27	6	22.2	21	77.8	19	70.4	10	37.0	6	22.2
Operation and x-ray	17	9	52.9	8	47.1	6	35.3	5	29.6	2	11.7
Irradiation	16	7	43.7	9	56.3	7	43.7	3	18.7	2	12.5
Not treated	2	2	100								
Total	120	26	21.7	94	78.3	81	67.5	40	33.3	26	21.7

Tumor Registry, some of these patients may live with cancer for more than 5 years. Several of these I have seen in consultation lived up to 10 years with relatively little discomfort.

To close my rather inadequate discussion of the many interesting problems touched upon by the essayists, I would like to call your attention to an important factor helpful in prognosticating the outcome of any form of therapy and that is to obtain fluid from the cul-de-sac in all surgically treated cases. Should this fluid reveal cancer cells, the outlook for survival is poor, and vice versa if none is discovered. I have followed this rule since about 1935 and I am convinced of its reliability.

DR. EDMUND OVERSTREET, San Francisco, California. Dr. Nash mentioned Stanley Way's interesting figure of incidence of endometrial polyposis in patients who have endometrial cancer. That figure is a very high one, and I doubt that it would be corroborated in other series. I should like to present a figure to you for future consideration, approaching the problems from another direction.

We have recently reviewed 400 consecutive cases of endometrial polyposis from our institution. The age distribution of those patients ran between 15 and 82 years, with the peak of the distribution curve in the fifth decade. Among those 400 patients there were 2 with carcinoma of the cervix, and there were 8 with carcinoma of the endometrium.

You will recall, from the figures of the California Tumor Registry, that in this state the ratio of carcinoma of the endometrium to carcinoma of the cervix is 1 to 2. In the cases of endometrial polyposis this figure is not only reversed, it is 4 to 1. Obviously, this small number of cases is not yet statistically significant. I hope it may become so when we read about 1,000

cases of endometrial polyposis. I think the finding is suggestive that some type of common etiological factor plays a role in the production of both endometrial polyposis and endometrial carcinoma.

Dr. J. George Moore, Los Angeles, California. I, too, have looked over statistics of therapy very carefully and have come to the conclusion that the statistical results of treatment will vary only minutely no matter how these patients are treated, as long as they are treated well and adequately. If statistics all over the world are studied, it will be noted that the Radiumhemmet, treating these patients by radiation alone, comes up with a figure of 63 per cent in the over-all 5 year survival rate. The Liverpool Radium Institute, treating endometrial carcinoma by hysterectomy alone, as Dr. McLennan does, proffers an entirely comparable figure. Other clinics, such as Dr. Arneson's, treating patients by preoperative radiation followed by hysterectomy, report survival figures which are almost identical.

All of these figures hide an inconsistency because as soon as the patients are subdivided into those with differing histologic grades and uterine size, as Dr. Traut indicated today and as Dr. Arneson has done in his analyses of these patients, we see that there are two groups of patients who do not respond well to treatment. These are the patients who have the anaplastic lesions and those who have an enlarged uterus. It has been our experience, and I know it has been Dr. Arneson's experience, that the patients who fall into these categories do better when they receive preoperative radiation than when they are subjected to hysterectomy alone. Evidently, Dr. McLennan has not been convinced.

Although I do not believe it has been published yet, Dr. Kottmeier states that the Radiu n-

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In mmet is abandoning radiation as the primary definitive treatment of endometrial carcinoma. They treat these patients primarily by hysterectiony with a postoperative radium mold. However, there are still two groups in whom Dr. Kottmeier does not employ hysterectomy primarily. These are the patients who have an enlarged uterus and those who have a highly anaplastic lesion. These patients are now treated, I believe, by preoperative radiation in full cancerocidal dosage—that is, 7,500 r to the serosal surface of the uterus. Also, those who have endometrial carcinoma in the cervix are placed in this category. Hysterectomy follows in 3 to 6 weeks.

We have independently come to the same conclusion and were somewhat surprised to have Dr. Kottmeier concur when we presented this approach in Seattle recently. There is one point where the Radiumhemmet will differ. That is in the patients who do not have undifferentiated endometrial cancer or who do not have an enlarged uterus and who will be treated by hysterectomy primarily. They will use postoperative vaginal radium therapy. The reason for giving this therapy is the very frequent recurrences in the vaginal vault and around the urethrasomething that we've all seen and found so distressing. Dr. Kottmeier feels that one of the best ways of preventing these recurrences is to use a radium mold in the vagina, attempting to deliver 2,500 r to a point 2 cm. deep to the vaginal epithelium by this radium mold. I would submit only that it seems more logical if you are going to employ radiation to give it while the blood supply to the pelvis is intact and while there is an adequate vehicle for the application of the radium—that is, use it preoperatively.

Dr. Purvis L. Martin, San Diego, California. Endometrial carcinoma is not now the killer of women that it once was. In San Diego County, where the Medical Society has organized a special project to eliminate deaths from uterine concer, only 22 people out of a population of a nillion people died of endometrial cancer in 199, according to Health Department reports. C rvical cancer, incidentally, killed only 30 San Diego women in 1959. Our efforts to eliminate deaths from uterine cancer appear to be bearing froit.

Advanced cervical cancer is a preventable disease today in that we have means at hand that if used can usually-prevent women from dying of this disease. Advanced endometrial

cancer is almost a preventable disease—not quite, because routine smears will miss one-third of presymptomatic cases, but almost. Most women can still be cured if the diagnosis is made soon after abnormal bleeding starts. Most of the 22 women who died of endometrial cancer in 1959 should not have died. A fatal error was made by someone in each such case.

So we made an attempt to find out who was at fault in each case. This was not easy since so many patients' illnesses were spread over several addresses, several doctors, several hospitals, and several years. However, it is apparent that most frequently it was the patient herself who erred. Either she did not avail herself of the routine smears that are widely urged for every woman in San Diego County or she did not report dangerous symptoms of abnormal bleeding soon enough. In several instances, however, it is apparent that physicians erred. Bleeding from fundal cancer was treated with hormones while the patient was being assured because her Papanicolaou smear was negative.

San Diego has developed one advantage over most other communities in preventing deaths from fundal cancer. Curettage in San Diego is usually an office procedure, and therefore can be done when indicated, without too much concern over cost, time away from work, and all the other problems involved in hospitalization.

Our study primarily reaffirms the importance of continuing programs of lay education and of physician education if our present project is to be carried to its ultimate goal, the prevention of all deaths from uterine cancer.

DR. RUSSELL R. DE ALVAREZ, Seattle Washington. Some problems relative to the incidence of carcinoma of the fundus have arisen in our community as a result of a review of the materials submitted to the Washington State Tumor Registry. There has been considerable variation in the reported incidence of carcinoma of the endometrium as related to the occurrence of carcinoma of the cervix. This distribution seems to run anywhere from equal distribution of carcinoma of the fundus to carcinoma of the cervix to a distribution ratio of 1 fundal to 5 cervical carcinomas.

Three opportunities arise for inclusion of the same patient material: (1) the material obtained at curettage; (2) the entry of the same diagnosis at the time of submission of the hysterectomy specimen; and (3) the inclusion of the tumor material at autopsy.

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In the Washington State Tumor Registry, the almost equal distribution of fundal carcinoma and cervical carcinoma may well be the reason why Dr. Martin can find only 22 deaths from endometrial carcinoma in a year in San Diego.

In this same connection, even though death certificates are notoriously unreliable, causes of death on death certificates are frequently spoken of as being simply cancer of the uterus. This terminology is used by some as being synonymous with carcinoma of the endometrium while with others it is synonymous with carcinoma of the cervix. I would make a plea that the reporting of carcinoma of the epithelial lining of the body of the uterus be as carcinoma of the endometrium, or fundus, or corpus.

Dr. CHARLES E. McLENNAN, Palo Alto, California. With regard to Dr. de Alvarez's comment on the statistics presented by the California Tumor Registry, I think they are probably not comparable to those of the Washington Registry if, as he indicated, the Washington material is to a large extent culled from death certificates. The data from the California study, reasonably carefully selected, comprise a prospective rather than a retrospective study and represent material from the current files of patients being treated in a group of hospitals, representing presumably the better hospitals in the state, carefully selected for this purpose. Thus, I think that we can have at least a modicum of faith in the arithmetic that appears on these particular sheets.

With regard to Dr. Moore's comment, he, of course, was trying to set up a friendly argument by implying that Dr. Arneson and I are on opposite sides of the fence. I don't think that really is the case. I am simply waiting around for the day when somebody will do an honest, controlled, clinical study of this situation and prove beyond a reasonable doubt that one or the other attack on the endometrial cancer problem is clearly a better way to approach it. It is interesting though, I think, that Dr. Kottmeier in Stockholm is now leaning somewhat toward the surgical side of the camp, and perhaps in a few years will be with us completely.

I fail to see, Dr. Moore, why the large uterus really makes much difference in this business. Why is the uterus large? Are these all uteri that are diffusely enlarged because of massive infiltrating tumor tissue, or are they simply uteri that were fairly sizable to begin with or uteri with varying number of myomas in them? I

don't believe we can put all the big uteri in the same basket.

The figures of Dr. Gusberg, which I alluded to in my prepared remarks, attack this point directly, but, as I tried to demonstrate, his colclusion was based on fallacious statistical reasoning, and yet some might say that because Guberg got a slightly higher cure rate with radium, this surely is the answer to the problem. I think we should continue to challenge this sort of statement. It would not be by any means impossible for a group of collaborating workers to undertake a really first-rate controlled study of the treatment of endometrial cancer, and certainly it would be extraordinarily easy, I think, for someone to initiate a controlled study of the simple question—is postoperative radium to the vaginal vault valuable? It should not be difficult to achieve truly random selection of patients and simply apply treatment according to a preconceived statistical plan over whatever time period may be required to accumulate convincing samples.

DR. HERBERT TRAUT, San Francisco, California. To say "carcinoma of the endometrium" is not to say anything really specific. There are 3 or 4 or 5 different types or grades, and the life cycles of these entities are quite different from one another.

The one outstanding fact with regard to endometrial cancer that has come as a result of the League of Nations reports is the difference between carcinoma of the fundus and that which involves the fundus as well as the cervix. But there are other differences. How are we, as gynecologists, to find out the difference? Your general pathologist as a rule will not tell you. How can anyone differentiate, or who can? For a long time there was a tradition, originating in Germany, whereby a gynecologist was also trained as an adequate pathologist. Today, we are not training people adequately in gynecological pathology. We must learn to recognize adenoma malignum, a very well-differentiated carcinoma of the endometrium, as compared to an anaplastic one, and there are gradations in between. When they are all grouped in one hodgepodge one cannot treat the patient arequately.

DR. HAROLD M. LYONS, San Francisco, Colifornia. If we draw a curve showing the p ak incidence of clinical carcinoma of the cer ix,

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the age incidence is in the middle forties. If we draw a curve of the incidence of carcinoma in situ of the cervix, the peak is in the middle thaties. As time passes, and the frequency of early diagnosis is increased, because of cytological detection, the invasive or clinical carcinoma curve will shift to younger age groups. It is important to remember that new techniques are the tools by which statistical curves are changed.

For the first time in my life I had a pathological report returned recently of preinvasive carcinoma of the fundus. It may well be that carcinoma of the corpus takes many, many years to become a clinical disease, recognized by both symptoms and signs, and that in order to treat these patients adequately and get a higher cure rate one would have to make the diagnosis earlier.

However, "early diagnosis" is not so simple as it sounds. The diagnosis of carcinoma of the cervix in the in situ stage is exceedingly difficult because the early lesions picked up cytologically are so exceedingly small that they are not found in routine small biopsy procedures. If you multiply the size of the cervix by the size of the fundus it becomes increasingly difficult to get an adequate sampling of the disease.

One of the interesting things about cytology is that the cells that are being desquamated are no longer active. When you see mitosis in a cell in a cytological smear, the cell is probably not malignant. Cells that are desquamated show up very readily in the posterior fornix. There is a general agreement among cytologists that the diagnosis of adenocarcinoma of the fundus is best made from smears taken from the posterior fornix.

The majority of patients who have adenocarcinoma have an increased estrogen response in the vaginal cells. I think this term "estrogen response" is important because there are a small group, as Dr. Emge pointed out to me, that do not have this increased estrogen response, and if you see malignant cells in those patients, you can be almost sure that the disease is an anaplastic type with a very rapid course. The fact that the vaginal mucosa shows an estrogenic response does not in any way prove that the individual has a higher estrogen level. She has either (1) a more sensitive vagina mucosa, or (2) some local source or reaction producing an estrogen-like quality.

We know that in squamous cell carcinoma

which has been ablated, malignant local cells are no longer produced. If the malignancy begins to grow in other parts of the body, the vaginal mucosa, in a period of time, will become cornified, regardless of the previous type of treatment. It is suggested that perhaps tumors within themselves have the ability to produce this type of phenomenon.

There are reportedly more recurrences of adenocarcinoma of the fundus in the upper vagina and around the urethra now than formerly. There has also been a remarkable change in the surgical approach to this disease. If a curettage is done on the patient, cells that are anaplastic and young are constantly fed into the vaginal canal and the possibility of implanting them at the time of operation increases tremendously.

I was trained to sew the cervix shut. It is reported some British surgeons also tan the vagina with gentian violet, dicric acid, or some other substance to prevent implantations of young malignant cells. Regardless of the method of operation, it should be looked upon as almost a type of infection, with possibilities of implantation. Certainly when a lot of young cells are being desquamated, you should do what you can to prevent this.

DR. AXEL ARNESON, St. Louis, Missouri. This may be a time for expressing a few convictions and certain propositions. I am convinced that one factor not included in this discussion is assessment of the human element. Differences in classification, as well as variations in effectiveness of treatment are certain to occur when a series of patients is collated from the experience of many gynecologists including some who treat cancer only occasionally. I am convinced that we should be concerned less with the reporting of survival results and more with a study of the disease as a whole. One cannot divide the management of cancer into separate steps of diagnosis, treatment, and follow-up.

Among the propositions I wish to suggest is that we present our studies with a maximum of clarity and with a maximum of uniformity in classification and in assessment of data. That will develop utilization of our knowledge of the disease. In cervical cancer, for example, there are differences in prognosis to be predicted on the basis of gross architecture of the tumor and in the tendency toward lymphatic spread. It is somewhat amazing to find extensive pelvic invasion sometimes without lymph node metas-

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tases. Those are the patients attaining longevity after pelvic exenteration. Control of cancer by that radical operation is rare among those with positive nodes. There are also useful points in assessing prognosis in corporeal cancer. Healy and Brown were the first to state the adverse prognosis for patients with enlarged uteri. That factor is more significant for treatment by irradiation, and Nolan has offered explanation on the basis of greater total volume of tumor.

Differences in maturation of tumor noted histologically are also associated with differences of prognosis.

Symposia of the order presented here develop the study as a whole. Perhaps we have deat inadequately with the statistical data presented the panel, but we have exchanged ideas in the attempt to form a meeting of minds on the management of corporeal cancer.

The clinical value of peritoneal lavage for cytologic examination

DANIEL G. MORTON, M.D.

J. GEORGE MOORE, M.D.

NORMAN CHANG, M.D.

Los Angeles, California

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> THE purpose of this investigation was to determine the cellular content of the peritoneal cavity as revealed by smears of the washings from the pelvic cavity obtained at laparotomy, and to evaluate the diagnosis and prognosis of various gynecologic conditions, especially ovarian tumors. Although we started our investigation independently, we soon become aware that others had attempted similar researches. The principal publications which have dealt with this subject are those of Keettel and Elkins² in 1956 and Keettel and Pixley1 in 1958 in which a study of 461 cases was presented. In addition, there have been a few casual references in the literature to the use of peritoneal lavage in connection with studies of chemotherapeutic agents for ovarian cancer but no comment as to its usefulness.

Abdominal washings (or lavage) have been obtained during all but a few laparotomies during the last several years in order to obtain experience. As soon as the abdomen was opened and before any manipulation, approximately 200 c.c. of sterile normal saline olution was squirted over the surfaces of the pelvic organs and the bowels in the lower

abdomen. The fluid which collected in the cul-de-sac was sucked up by a large bulb syringe. The same procedure was repeated at the end of the operation just before the abdomen was closed. Each specimen of fluid was centrifuged and the sediment smeared on a glass slide, and fixed and stained according to the Papanicolaou technique for vaginal smears.

From March, 1957, through June, 1960, 288 peritoneal lavages were studied. The

Table I. Indications for operations in cases in which peritoneal lavage was performed

Cancer of cervix (usually carcinoma in situ)	42
Cancer of endometrium	24
Infertility and nongynecologic conditions	27
Myoma of the uterus	54
Adenomyosis	2
Endometriosis	11
Pelvic inflammatory disease	17
Hydatidiform mole	2
Suspected neoplasm, not found	2
Ovarian cysts and tumors	84
Nonovarian, metastatic malignancy	17
Total*	283

*In 5 instances there were repeat laparotomies," making total 288.

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Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. reasons for the operations are recorded in Table I.

Serving to illustrate the "normal" cellular population of the peritoneal cavity were those patients with carcinoma in situ, infertility, myomas, and nonneoplastic cysts of the

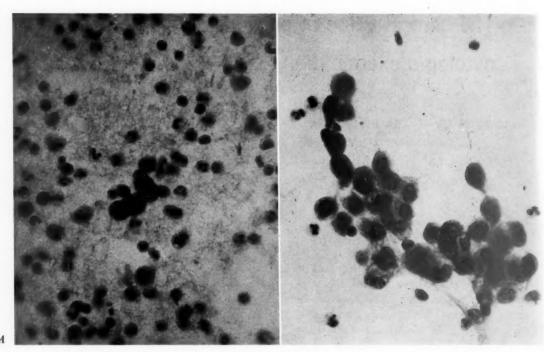


Fig. 1. Normal mesothelial cells. They are comparatively small, only 2 to 3 times the size of the polymorphonuclear leukocyte. They are characterized by round or oval nuclei containing fine to moderately coarse chromatin granules, and 1 or 2 small nucleoli. The cytoplasm is foamy and the cytoplasmic membrane is intact, although often indistinct. The cells stain a light greenish blue. A, The mesothelial cells lie in a field of leukocytes. B, The mesothelial cells are in a sheet.

ovary. The density of cellular population varied considerably but there was a considerable number of cells in the majority of the specimens. In these control cases, mesothelial cells, leukocytes, and macrophages were the principal cells found (Fig. 1). Red blood cells were seen frequently, and squamous cells were seen occasionally. The latter were more common in the specimens obtained at the termination of operation. It was our deduction that these cells represented contamination from the skin wound. There was considerable variation in the appearance of the mesothelial cells which has been noted frequently by others (Fig. 2).

The postoperative specimens were obtained specifically to determine whether there was a "spill" of cells in the removal of malignant tumors of the pelvic organs. In all of our cases the postoperative specimens were almost always "cleaner" than the preoperative ones.

With respect to pelvic malignancy, smears of abdominal washings were regarded as positive or suspicious in 25 of the 35 patients in whom malignant tumors were present. ! Examples are shown in Fig. 3. In 10 instances a false-negative result was obtained; in 3 of these cases the tumor was well confined clinically; and this might have meant that the malignant areas were, in fact, confined and that a good prognosis was indicated. The other 7 represented instances of metastatic malignancy, 4 from the cervix, 1 from the colon, 1 from the breast, and from an unknown source; there were retroperitoneal masses in lymph nodes which would not have been expected to shed cells into the peritoneal cavity. In 7 of the 253 cases in which no malignancy existed in the peritoneal cavity, the smears were called positive. In 4 of these patients the operations were performed for endometrial cancer and in 1 patient for cervical cancer. Whether

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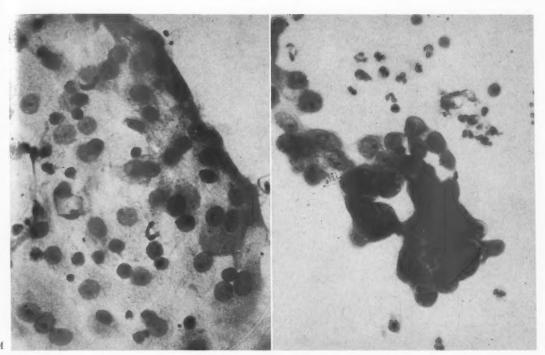


Fig. 2. Atypical mesothelial cells. There are a number of variations of which two are shown in A and B. The cells may vary markedly in size and shape and hyperchromasia may be present. The nuclei may appear irregular and double. Multiple nucleoli are seen frequently. Sometimes the cytoplasm appears quite dark. Engulfed white blood cells and molding of cells are sometimes seen. A form not illustrated is that of sheets or strands of small oblong, darkly staining but rather uniform cells. A, Sheets of mesothelial cells containing vacuoles and engulfing white blood cells. B, Molded, hyperchromatic mesothelial cells.

cells from these tumors got into the abdominal cavity by way of the tubes, or whether they were simply interpreted erroneously cannot be said with certainty. We, as well as others, have found cancer cells from endometrial cancer by washing them out of the oviducts postoperatively so that the finding of cancer cells in the peritoneal cavity was not completely unexpected. Presumably the other 2 cases were simply errors of interpretation (Table II).

Keettel and Pixley¹ reported similar results: in 30 of their 461 cases the peritoneal washings were positive. Twenty-five of their patients with positive cytology had ovarian carcinoma. Three patients with positive cytology had benign lesions. In their group of 45 ovarian carcinomas, the cytologic findings were positive in 24 and suspicious in 9.

Another approach to evaluating the accuracy of peritoneal lavage in detecting

Table II. Correlation of cytologic findings with the presence or absence of cancer in the pelvic cavity

	Interpretation of smears					
Pelvic findings	Classes I and II, "negative"	Class III, "suspicious"	Classes IV and V, "positive"	Total		
ancer in pelvic cavity	10	6	19	35		
to cancer in pelvic cavity	246	4	3	253		
otal	256	10	22	288		

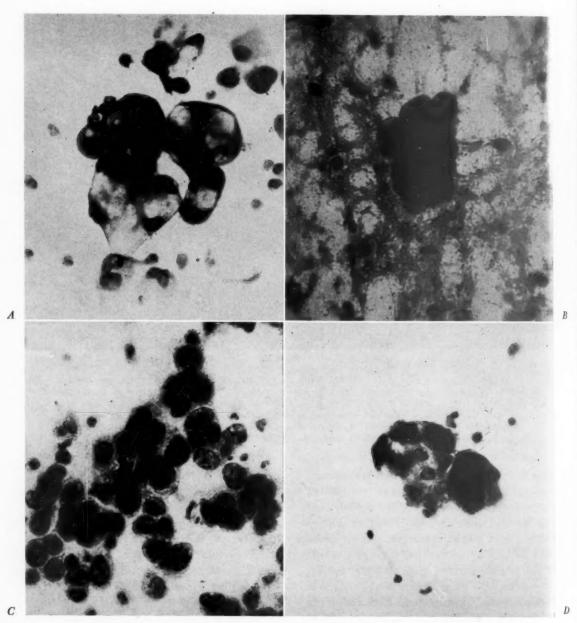


Fig. 3. Examples of peritoneal smears from patients with malignant ovarian tumors. A, From patient with serous cystadenocarcinoma; the cells are enlarged 3 to 5 times that of the normal mesothelial cells. The nuclei are hyperchromatic and contain coarse chromatin granules and enlarged or multiple nucleoi. The cytoplasmic membranes are distinct and there are large multichambered vacuoles present. B, From patient with a malignant teratoma; the cells are enlarged and molded, and contain many mitotic figures and nucleoli. They stain well with periodic acid—Schiff reagent. C, From patients with poorly differentiated papillary serous cystadenocarcinoma; the cells are moderately enlarged and contain irregularly shaped nuclei containing very coarse chromatin granules. Nucleoli are prominent and enlarged. Only a small amount of cytoplasm surrounds the nucleus. The cytoplasmic membrane is indistinct in many cells. D, From a patient with pseudomucinous cystadenocarcinoma; the cells are enlarged, molded and contain hyperchromatic nuclei. The cytoplasm is moderately dense and the cytoplasmic membrane is distinct. (Original magnification ×200.)

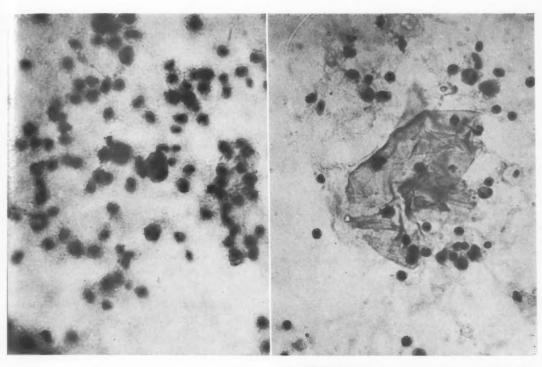


Fig. 4. Cells from benign ovarian tumors. A, The smear was obtained from a patient with a dermoid cyst of one ovary and shows occasional small cells of irregular or oval outline with acidophilic cytoplasm and distinct cytoplasmic membrane which are unlike any of the cells seen in "normal" cases. These cells are thought to be epidermoid. B, By way of comparison squamous cells thought to come from the abdominal skin are shown. C, Tumor cells found in association with a benign pseudomucinous cystadenoma show round or oval nuclei crowded to one end of the cells. The cytoplasm is moderately dense and somewhat opaque in appearance. The over-all appearance suggests that of the characteristic cells of pseudomucinous tumors.



nalignancies in the pelvis is illustrated by he figures shown in Table III.

For the small number of cases involved would appear that peritoneal lavage gave he correct answer when the tumor was a rimary ovarian one in a very large proporion, indicating, unfortunately, that cancer cells have usually penetrated the capsule even though the tumor is clinically well confined. The negative result *might* indicate a good prognosis. With respect to nonovarian, metastatic malignancies in the pelvis, the results were not reliable. The varieties of primary ovarian tumors are given in Table IV.

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Table III. Correlation of cytologic findings with the ovarian or other pelvic cancer

Primary ovarian malignancy			14
Positive lavage	13	(93%)	
Negative lavage	1		
Nonovarian and/or metastatic			
cancer			21
Positive lavage		(55%)	
Negative lavage	9	(47%)	
Total malignancies			35

Table IV. Varieties of the primary ovarian tumors encountered

Type	Benign	Malignant	No.
Serous	5	10	15
Pseudomucinous	7	2	9
Teratoma	13	2	15
Gonadoblastoma			1
Unclassified		1	1

In some instances it was thought possible to identify tumor cells of the benign ovarian tumors (Fig. 4). We are uncertain of the reliability of our interpretations in these respects and fail to understand why tumor cells should shed from the exterior of benign tumors.

In Table V the findings at lavage are correlated with the various ovarian tumors whether they were smooth externally and freely movable or whether they were adherent or showed external papillae.

Of the 23 primary ovarian tumors which were externally smooth and freely movable, i.e., clinically and grossly benign at operation, 21 were actually benign and there were no false-positive smears obtained in these cases. In 7 of the 21 it was thought that benign tumor cells could be identified. In the cases of the 2 externally smooth, freely

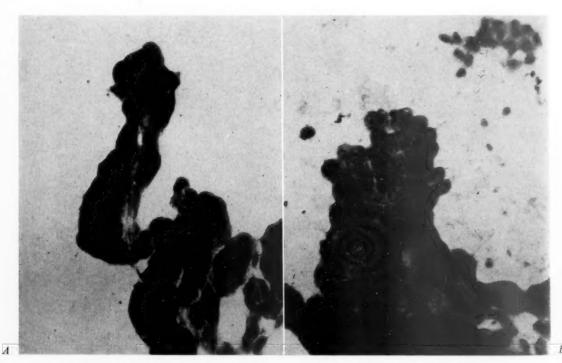


Fig. 5. Endometrial cells. The cells occur in clumps (A) and sheets (B) of closely packed cells, often in multiple layers. There is a pronounced tendency to molding. The nuclei are round or oval and contain finely granular chromatin. Nucleoli may or may not be present. The cytoplasm occurs as a narrow layer surrounding the nucleus, and is moderately dense and stains a blue green with the staining technique employed. These cells look like those obtained by endometrial layage.

Tible V. Correlation of cytologic findings with the physical characteristics of the various ovarian tumors

		Find	ings in lavage	fluid
Kind of tumor	Total	Carcinoma cells	Tumor cells	Neither
Serous, benign				
Externally smooth, free, no adhesions	3			3
Externally free, adherent	2		1	1
Serous, malignant				
Externally smooth, free, no adhesions	1			1
Externally smooth, adherent	2	1	1	
With peritoneal implants	7	7		
D Jamusinaus hanian				
Externally smooth, freely movable	5		3	2
Externally smooth, adherent	2		J	2 2
Externally smooth, adirective	2			4
Pseudomucinous, malignant				
Externally free, movable	1	1		
Teratomas, benign				
Well contained, freely movable	12		4	8
				_
Teratomas, malignant	2	0		
Not contained clinically	2	2		
Unclassified, malignant				
Not contained clinically	1	1		
Gonadoblastoma	1			
Well contained, freely movable	1			1

movable malignant tumors, one was associated with a positive peritoneal lavage smear and the other was not. In the Keettel and Pixley series there were 5 individuals with ovarian cancer without visible evidence of breakthrough of the capsule, no free fluid, and no omental or peritoneal implants, but with positive smears of the peritoneal washings.

The cases of metastatic malignancy are not analyzed in detail. There were 19 such, 11 of which were associated with positive smears. The primary tumors were in the endometrium, cervix, breast, and digestive tract, and 2 were of unknown/origin.

Of corollary interest were the cases of endometriosis classified in Table VI. In 8 of the 15 cases, cells were found in the lavage stream which were interpreted as endometrial cells (Fig. 5).

Comment

Our observations need to be extended in order to provide a full evaluation of the

cytologic characteristics of smears from the peritoneal cavity in connection with questionable cases of pelvic malignancy. It is logical to assume that ovarian cancers with external papillae or breaks in the capsule might well shed malignant cells into the peritoneal cavity. It is less clear as to how malignant ovarian tumors with intact capsules could do this. It seems clear that the presence of malignant cells has a definite connotation so far as primary ovarian tumors

Table VI. Cytologic results correlated with pelvic endometriosis

Endometriosis	No. of cases	Endo- metrial cells found	No endo- metrial cells found
Confined to ovaries Implants in peritoneal	8	2	6
cavity	6	5	1
Confined to appendix	1.	1	
	15	8	7

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are concerned. This type of examination is definitely not an aid in *early* diagnosis but may be of value when the nature of a smooth-walled, freely movable cystadenoma or other intact ovarian tumor is questionable. The absence of malignant cells under such circumstances may indicate a good prognosis. More cases and more time will be necessary to establish this point.

The significance of malignant cells in the peritoneal cavity beyond the diagnostic and prognostic implications is not clear. Are such cells invariably viable? Would they always result in peritoneal implants? There is no positive answer available. Like malignant cells in the blood stream, they may not always mean a metastatic development. Yet their presence in the peritoneal cavity would make one feel that radiation therapy, chemotherapy, or both were indicated postoperatively, no matter how favorable the immediate operative removal appeared to be.

Keettel attempted to develop this general technique as a diagnostic aid by injecting a small amount of sterile saline solution into the cul-de-sac, through the posterior vaginal fornix, and withdrawing it for smearing and cytologic study. In 247 cases his results were completely negative. However, quite recently we heard Dr. Ludwig Emge observe that he had used such a technique in a number of cases, and that it had permitted him to make a positive diagnosis of cancer preoperatively when it could not possibly have been made in any other way. We believe that this or a related technique has some valuable possibilities in making diagnoses in obscure cases.

We are also interested in the fact that

cancer cells from endometrial cancer get into the tubes and are occasionally found in the peritoneal cavity. Endometrial cells have also been found in smears of peritoneal washings in association with endometriosis but, in the instance, it is not possible to state which scause and which is effect.

Summary and conclusions

- 1. Peritoneal washings at laparotomy were examined cytologically in 288 cases.
- 2. In the 35 cases in which a malignant tumor was present in the pelvis, positive smears were found in 25. The 10 false-negative smears were associated with well-confined tumors or metastatic tumors.
- 3. In 7 instances positive smears were obtained when there was no malignancy in the pelvis clinically. In 4 of these cases the operation was for endometrial cancer and in 1 for cervical cancer.
- 4. There were 14 cases of primary ovarian malignancy of which 13 were associated with positive peritoneal smears. The percentage of positive smears in association with metastatic pelvic cancer was approximately 50 per cent.
- 5. Of 23 primary ovarian tumors, clinically benign, 21 were actually benign and there were no positive smears associated with these cases. In the cases of the 2 clinically benign malignant tumors one was associated with a positive peritoneal smear and one was not (a questionably good prognosis).
- 6. It appears that this procedure has a certain diagnostic and prognostic value, especially in relation to primary ovarian tumors, which are externally smooth and freely movable.

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- Keettel, W. C., and Elkins, H. B.: Am. J. OBST. & GYNEC. 71: 553, 1956.

Discussion

Dr. R. Glenn Craig, San Fancisco, California. Our clinical experience in the past has led us to believe that a well-encapsulated malignancy in a cystadenoma offers a good prognosis without postoperative radiation. In this study the e were positive smears in patients who were considered to have a good prognosis. Cole and othe showever, have reported malignant cells in the 5)

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 \pm pod stream which have not resulted in metastases. Positive smears are disturbing but are \pm as "positive" as the word implies.

Radiation is not an innocuous procedure and should not be administered without good reason. A 1 or 2 per cent increased survival rate is a good indication. Many may be inclined to establish a routine which may contribute to the discomfort of the patient without increasing the chances of survival.

Dr. Morton has used lavage. Is there not enough fluid normally present in the cul-de-sac to provide a more concentrated and accurate method, or would a smaller volume for lavage be more convenient and accurate when necessary?

There were 2 patients with hydatidiform moles in this series. I wonder if cul-de-sac punctures and washing would be useful in suspected choriocarcinoma.

I recently heard of a patient who had a vaginal hysterectomy but died 6 months later from a carcinoma of the stomach or pancreas. Would peritoneal cytology have been of value in this case or other cases of vaginal hysterectomy?

Dr. Ludwig A. Emge, San Francisco, California. I strongly urge you to familiarize yourselves with this method, or the more simple one which I have used since 1935, I do not go to the trouble of lavaging the peritoneal cavity, but as soon as the abdomen has been opened, I obtain whatever fluid is present in the cul-de-sac and in the space of Retzius. To do this I use a 10 c.c. syringe to which a simple blunt adapter has been attached. The material obtained is put into a test tube and sent to the laboratory for cell study, regardless of pelvic findings. In the case of actual or suspected malignancy of the ovaries or, for that matter, of any kind of malignancy of the pelvic organs, the cellular elements found will tell if the disease has spread into the abdominal cavity. It does not, however, whether or not the disease has entered the imphatic system. To ascertain that possibility, mphadenectomy is necessary.

Occasionally one encounters an element of s rprise when following this approach to progressis. Not long ago, I obtained a considerable amount of blood-stained fluid from the cul-desc in the presence of a large fibroid tumor. There was no evidence of any demonstrable malignancy in the pelvis and bowel, and there were no palpable abnormalities in the upper andomen. The pathologist reported the presence

of adenomatous structures, evidently malignant, present in the fluid obtained. Six months later the patient developed symptoms indicative of pancreatic malignancy. Surgical exploration confirmed this and the patient succumbed soon after this. A comparison of the tissue obtained at autopsy and the glandular elements seen in the cul-de-sac fluid left no doubt as to their common identity.

The method under discussion is valuable from three points of view:

- 1. Negative findings exclude the presence of abdominally disseminated cancer and definitely favor a good prognosis, barring the involvement of the lymph nodes.
- 2. Positive findings indicate that cancer has disseminated widely, definitely pointing toward an unfavorable prognosis, at the same time suggesting the need for irradiation or chemotherapy. I have yet to see a patient who did not ultimately succumb to cancer regardless of the type of postoperative therapy whenever cancer cells had begun to range the abdominal cavity.
- 3. Then there is a third element, the element of surprise, which I have described. It demands a thorough search for the unknown source albeit success in discovering it may be remote.

I must mention that in the presence of ascites, a simple cul-de-sac puncture through the posterior vaginal fornix is an equally informative method to learn about the possible presence of malignant disease and its probable origin. If findings are positive, transabdominal irradiation should precede any attempt at surgical removal. Whether you will follow Dr. Morton's advice or the methods I have mentioned, matters little. The important point is that what Dr. Morton has advocated is an essential step forward toward better prognosis in case of pelvic malignancy.

Dr. Herbert F. Traut, San Francisco, California. May I tell you about one patient, whom I have had to deal with in the last 2 or 3 years, who shed or produced cells, which were recognized in the ascitic fluid from a uterine sarcoma. This was a mesodermal type of sarcoma which had been recognized before and which recurred and was inoperable at the time we saw her. We proceeded to shrink the growth with x-ray treatment, so that eventually it could be resected. However, before we tampered with it at all we collected some of the ascitic fluid, spun it down, fixed it, and looked at it under the microscope. Much to our surprise we found connective tissue

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cells. There were metastases widely spread on the surface of the bowel, identified at a later laparotomy. It is very difficult for me to understand the mechanism whereby this came about.

Of course there is also the work of Javert in New York, with a demonstration of endometriosis, not only on the surface of the peritoneal organ, but in the lymphatics. We have a great deal to learn about the life cycle and the transmission of cancer cells, epithelial cells, and apparently also of connective tissue cells.

Dr. Woodburn K. Lamb, Berkeley, California. In the past 20 years, treatment of endometrial and cervical carcinoma has shown advances in the salvage rate but ovarian carcinoma has remained essentially the same. This has been due to a large extent to our lack of diagnostic aids for ovarian carcinoma, and studies such as Dr. Morton's lend some hope that this particular phase may be changed.

In 1958 Keettel and Pixley reported 461 cases of peritoneal washings. Thirty patients revealed positive cytologic smears, 25 of whom had ovarian carcinoma. Three were endometrial carcinomas and 2 were benign. They reported 18 suspicious smears from the cytologic viewpoint and, of these, 9 proved to be histologic ovarian carcinoma, 8 arose from benign tumors of the pelvis, and 1 case revealed peritoneal implants from endometrial carcinoma. There were 6 cases with frank ovarian carcinoma in which the smears were negative from the cytologic viewpoint.

A most interesting point to me was that 5 of the patients who had positive cytologic smears showed no carcinoma from the viewpoint of gross inspection. These later proved to have carcinoma of the ovary from the histologic viewpoint. Three of these tumors were papillary cystadenocarcinoma and 2 were pseudomucinous adenocarcinoma. As this technique becomes more familiar and used, a problem is going to arise as a result of the finding of suspicious or positive smears, where the ovary has been negative from the gross viewpoint.

Dr. Russell R. de Alvarez, Seattle, Washington. Dr. Morton indicates the presence of 7 false-positive smears, all but 2 of which were accounted for in the histopathology. Out of 25 positive smears, this would be an incidence of 8 per cent false positive which is quite high. We have changed our designation from false-positive

to conditionally positive smears, meaning the malignancy probably is present somewhere within the patient's peritoneal cavity or elsewhere by has gained access to the peritoneal cavity and may, therefore, be perceived in the smears. We have had the opportunity to report on the diagnosis of ovarian carcinoma, carcinoma of the stomach, carcinoma of the gall bladder, and of other carcinomas which have metastasized to the peritoneal cavity, through vaginal cytological means.

In addition to the cytologic findings in the peritoneal fluid, I am sure that Dr. Morton has taken simultaneous posterior vaginal pool and cervical smears from these same patients; it would be interesting to know the results of a comparative analysis of the positive smears from the peritoneal fluid with those from the vagina.

DR. MELVIN W. BREESE, Portland, Oregon. I simply wanted to ask Dr. Morton if tissue culture studies of these malignant cells from the ascitic fluid have been made, and if he feels that this technique would give us some ideas of whether they would grow or metastasize.

DR. RONALD NIELSON, Portland, Oregon. Dr. Morton mentioned early in his paper that he took aspirated fluid at the beginning and at the end of each operation, and I wonder if the comparison of the two yielded any information.

Dr. Donald Harrington, Stockton, California. I would like to ask Dr. Morton a question. He had 16 cases, I believe, of carcinoma of the fundus. Out of these he got 4 positive aspirations from the abdominal cavity. It is a known fact that tumors have varying rates of desquamation. For example, cancer of the cervix obviously desquamates at a very high rate, therefore, we get a very high rate of return on a Papanicolaou smear. Cancer of the fundus apparently does not desquamate at such a high rate; we, therefore, get a much lower return on our smears. Yet cancer of the fundus tends to implant on the peritoneum at a higher rate than does cancer of the cervix. Normal endometrium tends to inplant as noted in the washings in his cases endometriosis. I am interested in knowing whether these washings, in cases of cancer of the fundus, followed curettage.

DR. MORTON (Closing). I do not know about the application of tissue culture to peritone I

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lim. he ra-MI lasly we OIL ot re, T t he wishings but Dr. Moore can answer the question. (emparison of aspiration at the beginning and at the end of the operation has not told us much. As a matter of fact, we have obtained much heavier cell populations in the first specimen than we have in the second, possibly because of having washed out all the cells preoperatively.

Of course we have always curetted patients with endometrial carcinoma, but usually some time before the laparotomy. When the diagnosis was made, radium was put in. We usually precede our operations with intrauterine radium, but then we let 6 weeks elapse before hysterectomy. However, I have no doubt at all that curettage may spread or push cancer cells out into the peritoneal cavity, and into the circula-

Just one case that shows the problem: A patient that I have in the hospital right now, a young woman of 35, never pregnant, came with an ovarian cyst which appeared to be something about 15 cm. in diameter. At operation it appeared to be perfectly smooth and perfectly free and the other ovary and uterus were entirely normal in appearance. We took out the one tube and ovary and opened the cyst at the table, which I think we should always do in spite of the fact that our pathologists do not like us to do this because it ruins the specimen. This tumor had some superficial papillary processes on the interior, which on frozen section appeared to me to be definitely malignant. The preoperative peritoneal washing, in this case, before we had done anything else except open the abdomen, was cluttered up with malignant cells. Well, what are we going to do with such a case? Naturally, we must treat the patient chemotherapeutically, with thio-TEPA or something of the kind, and possibly with radiation too. I would like to be able to see what would happen to this patient without further treatment, but my conscience would not permit that.

Genital tuberculosis in women

KARL L. SCHAUPP, JR., M.D.

San Francisco, California

FEMALE genital tuberculosis is not a common disease in the Western United States but it does exist and the diagnosis is usually missed clinically. It is found more often in Continental Europe, the British Isles, South America, and Israel. It is the purpose of this paper to outline the cases occurring in two San Francisco hospitals in the last 10 years or so. The cases were taken from the diagnosis files of Stanford (12 cases, 350 beds) and of Children's Hospital (7 cases, 258 beds). There were a few additional cases which were eliminated because the tissue came from women attending the outpatient clinic and there was no operation or followup. These were usually endometrial biopsy specimens from infertility patients.

Material

The salient features of these 19 cases were as follows: The youngest patient was 22 years old and the oldest 49. There were 4 Negro, 1 Chinese, 1 Spanish, and 13 white patients. There were only 4 patients who had histories of term pregnancies, with a total of 8 deliveries. There were 5 patients with a history of miscarriage and 1 of these was among those who had had term pregnancies. One patient had never been married. There was a past history of tuberculosis in 5 and an additional patient had had pleurisy. The chest film was positive in 2 patients after

the diagnosis of pelvic tuberculosis had been established. The most common complaints were pelvic pain,10 menorrhagia,6 irregular vaginal bleeding,4 and infertility.2 The most common findings were those of pelvic inflammatory disease7 and pelvic tumor8sometimes combined. These were also the most common preoperative diagnoses. The postoperative diagnoses indicated a suspicion of tuberculosis three times. Tuberculosis was diagnosed only twice without the help of a preceding biopsy. The operations varied from biopsy to total removal of the pelvic organs. Total hysterectomy and bilateral salpingo-oophorectomy was done nine times and supravaginal hysterectomy and bilateral salpingo-oophorectomy was performed five times. One patient had a negative tuberculin test with tuberculous pelvic inflammatory disease and pulmonary involvement. In 17 cases the Fallopian tubes were removed and 13 of these showed a granuloma compatible with tuberculosis. In one case, pyosalpinx and salpingitis (nonspecific) was diagnosed under the microscope and it was not until 6 weeks later when a forgotten culture was reported positive that the correct diagnosis was made. One patient had negative tubes although the ovary was positive. The ovaries were positive in 6 cases and not available in 5 cases. The myometrium was available in 14 cases and was positive in 3. The endometrium was available in 17 cases and was positive in 10. The cervix was present in 9 cases and positive in Associated pathologic condition was myoma in 3 cases and a thecoma in 1.

Bacteriological studies were done in 10

From the Stanford University School of Medicine.

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. cases. Cultures were done six times (including 2 urine and 1 gastric specimen) and were positive in one patient. Stains were made and one was positive. Guinea pig inoculation was done three times with no positives.

Treatment

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Treatment was varied. Five patients received no antituberculosis treatment. All but of these were seen in or before 1953. Five patients received 3 drugs (streptomycin, para-aminosalicylic acid, and isoniazid), 4 received streptomycin and para-aminosalicylic acid, and 1 received streptomycin and isoniazid. Of the patients with no treatment, 1 died 3 years later of embolism from severe rheumatic heart disease. There was no autopsy but there had been no further evidence of tuberculosis. The rest did well with follow-up periods from 6 months to 10 years with an average of 5 years. All but 1 (who had a recurrence) of the treated group did well with a follow-up period of 4 months to 14 years, averaging 5 years. Four patients with no treatment had incomplete operations, 1 died (the patient with rheumatic heart disease). The rest remained well for 10 years, 8 years, and 8 months, respectively.

Patient H. W. is the only one who had a recurrence and this case illustrates what can happen over a long period of time. In 1946, she underwent laparotomy with a diagnosis of pelvic inflammatory disease, probably tuberculous because she had a history of tuberculosis in 1944. She proved to have multiple abscesses and adhesions and, aside from removal of a tube, these were inoperable. The tube confirmed the diagnosis of tuberculosis and she went to the San Francisco Hospital Tuberculosis Division where she received streptomycin for 3 months and spent 6 months in the hospital. Endometrial biopsy in 1949 showed tuberculosis and she was given another course of treptomycin. Curettage after this course of therapy showed no remaining tubercuosis. A pelvic examination at this time howed a normal sized uterus which was a ittle fixed, but there were no adnexal masses. In October, 1955, she began to have recurrent abdominal pain which eventually required hospitalization in December with a diagnosis of pelvic inflammatory disease. On dismissal she was put on a course of PAS, INH, and streptomycin and then underwent a second operation on Feb. 21, 1956. There were many dense adhesions and the operation was technically difficult but total hysterectomy, bilateral oophorectomy, and of the remaining tube were done. Microscopic examination showed only chronic old healed minimal salpingitis. There was no evidence of tuberculosis. She recovered quickly and said she felt better than she had for many years. She has remained well to the present time.

Comment

There seems to be an incidence of about 1 case of female genital tuberculosis per year on an active gynecological service in an average sized hospital in San Francisco. The disease occurs mostly in the third to fifth decades in this series and there is a high proportion of Negroes. As in other reported series there is a poor obstetrical record and also a high incidence of pulmonary tuberculosis. There is no specific symptom or physical finding, but chronic recurring pelvic inflammatory disease resistant to the usual antibiotics, especially if there is a history of tuberculosis, should arouse suspicion. The surgical treatment can be individualized but the course of the disease does not seem to be quite as severe as in other reported series from other countries. Perhaps our general level of health is better. Operations in severe cases may be difficult, and definitive operations may have to be postponed. The Fallopian tubes are almost always involved, the endometrium being the next most common site of involvement. It is not possible to demonstrate the organism in all cases, and the diagnosis may be made on the basis of the findings under the microscope alone. Other granulomas attacking the pelvic organs are extremely rare. Treatment in the earlier cases in this series did not have the advantage of the antituberculous drugs. Since 1953, in this series, these drugs have been used with great success. The outlook for life is excellent. The outlook for successful pregnancy is poor.

It is interesting to note that the tuberculosis wards at the San Francisco General Hospital have not been a source of cases. Reports indicate that up to 20 per cent of women with pulmonary tuberculosis will have positive cultures of menstrual blood. Undoubtedly, there have been many asymptomatic cases, but the antimicrobial agents have suppressed the pelvic manifestations.

Female genital tuberculosis is always considered to be a secondary infection. The primary lesion is usually in the lungs. The higher incidence in other countries used to be explained on the basis of poor milk supply and bovine tuberculous infections of the abdominal lymph nodes. Arthur M. Sutherland³ of Glasgow, Scotland has identified the organism in his area in a number of cases and it proves to be the human strain. The explanation then must be in the better general level of health in the United States. The Fallopian tubes are the most vulnerable of the pelvic organs and apparently become infected with the bacilli 6 weeks to 6 months after the initial infection. They are resistant to infection in infancy and in childhood and seem most susceptible in adolescence and early maturity, becoming resistant again with maturity.1,2 The infection is usually present some time before it is diagnosed.

In asymptomatic cases the diagnosis is usually made by endometrial biopsy in the routine work-up of an infertility study. Cultures of menstrual blood will also reveal these cases. Symptomatic cases are not commonly diagnosed in San Francisco or probably not anywhere on the West Coast. If the disease is suspected, biopsy and/or culture can be used to make the diagnosis so that the proper therapy may be started.

Therapy will be decided by the degree of involvement of the pelvic organs, the patient's age, parity, emotional make-up, and general health. Asymptomatic disease with negative pelvic findings can be treated with antimicrobial agents and the patient

followed closely. The presence of pelvice masses probably means that an operation should be done. The best operation for cure is total removal of the pelvic genital organ and the minimal acceptable is bilateral sal pingectomy. Antimicrobial agents should be used preoperatively for 2 to 4 months and postoperatively 1 to 2 years depending or the severity of the disease. Cultures and sensitivity tests are available and should be done if possible. The currently most commonly used drugs are streptomycin in doses of 1 Gm., intramuscularly two times per week; isoniazid in doses of 100 mg. three times a day; PAS, 12 Gm. a day in divided dosage. Most reports on female genital tuberculosis recommend using all three but physicians who have treated the disease at the San Francisco General Hospital for years say that there is no advantage of three drugs over two. Resistance develops rapidly to one drug so two must be used. Two new drugs are pryazinoic acid amide and cycloserine, but they are toxic with effectiveness limited to 2 to 3 months. They are used only when there is resistance to other drugs. Adrenal steroids used in conjunction with other drugs may help prevent damage and scarring. There have been no reports on the use of the last three drugs in female genital tuberculosis.

Summary and conclusions

A series of 19 cases of female genital tuberculosis from two private hospitals presents about the same clinical picture and course as in other reported series.

The treatment of the disease improved greatly about 1953 with the expanded use of potent antimicrobial agents. Treatment should be decided upon the basis of the stage and severity of the disease and the age, parity, and general health of the patient. Antimicrobial agents should always be used —and for a long time (1 to 2 years). They may be used alone or in preparation for operation and in follow-up care. Patients should be followed indefinitely.

The outlook for successful pregnancy is poor and the prognosis for survival is good

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Discussion

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DR. ERVIN E. NICHOLS, Los Angeles, California. In discussing the treatment of the 19 patients, Dr. Schaupp classified the cases into several groups with respect to the type of chemotherapy. It is suggested that the group without chemotherapy did not do as well as the treated group, in that there was 1 death in this series. However, it is to be pointed out that this patient died of an unrelated disease.

Some of the reasons that make this disease difficult to treat are:

- 1. The tubercle bacilli have a tendency to become resistant to an antibiotic if they can continue to grow or multiply in the presence of small concentrations of the drug.
- 2. In tuberculosis, the blood vessels have the tendency to become obliterated and this causes a further decrease in the concentration of any chemotherapeutic agent.
- 3. In the progress of this disease, there is a tendency to caseous degeneration which has no blood supply. Thus the organisms within the caseous area are free to multiply further.
- 4. In tuberculosis the bacilli continue to live within the macrophages and the antibiotic agents are unable to penetrate the cellular membrane.

Probably the most important agent now being used is isoniazid. The action of this drug is primarily bacteriostatic and it is important to note that one of the definite advantages of isoniazid is that it can attack the bacilli within the macrophages. This drug does have toxic manifestations in that with long periods of treatment patients may be troubled with peripheral neuritis. It has been suggested that the peripheral neuritis may be prevented by the concomitant se of pyridoxine, but it should be noted that one of the major antagonistic agents to isoniazid is yridoxamine which is a breakdown product of yridoxine. This suggests that the possible relief of the neuritis may also result in a less theraeutic effect of the drug. Thus, an attempt should made to treat these people as long as possible without the use of pyridoxine rather than to give it on a prophylactic basis.

The next most important drug is streptomycin which is reasonably familiar to all. It is known

that streptomycin has a tendency to attack the eighth nerve and one of the side effects of long usage of streptomycin is dizziness. If this drug is being used while the patient is ambulatory it should be given at the end of the day so that the dizziness will not affect the patient's normal activity.

The third drug is para-aminosalicylic acid commonly known as PAS, which is the most expensive, the least effective, and the most toxic drug in that it can cause purpura, hepatitis, and encephalitis. However, when this drug is used in combination with the one or the other of the two previously mentioned drugs, it has a very definite synergistic action in that it tends to delay the formation of bacilli resistant to the one or the other drugs that are being used.

Pryazinoic acid amide, one of the newer drugs being tried, has severe toxic properties, one of which is a propensity for causing liver damage. The antibiotic cycloserine is definitely hazardous in that it causes central nervous system toxicity.

The question of whether a patient should or should not be operated upon always is a difficult one to decide. However, if the patient presents any symptom referable to the pelvis that cannot be controlled by chemotherapy or if there are persistant pelvic findings of tenderness and/or masses, the patient should be operated upon and the source of the infection removed. In the cases of chronic pulmonary tuberculosis, the treatment now is considerably less conservative in that the patients are operated upon much sooner in order to remove the source of recurrent infection.

Dr. Richard L. Taw, Los Angeles, California. I would like to add a word about the incidence at the Los Angeles County Hospital. For a number of years we were seeing an average of 6 patients with tuberculosis of the pelvis each year, and these usually presented themselves with an acute inflammatory condition, and not all of them got well. Between 15 and 20 per cent died.

Often these patients are infertile, but occasionally bizarre things happen. I remember an instance of a woman who was seen after being

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delivered of a term infant, with a uterus approximately the size of a 7 months' gestation. She had been delivered of 2 previous term infants, both of whom died of tuberculosis. The recently born infant and the patient herself eventually died of tuberculosis. This patient, then, was able to carry 3 pregnancies to term in spite of genital tuberculosis.

Dr. Robert K. Plant, Seattle, Washington. Until very recent years tuberculosis of the female genital organs was considered a very rare form of tuberculosis. This has been due to the fact that the disease was never diagnosed except in the exudative form-in other words, a form of the disease where it may be palpated or observed at the time of operation. Perhaps some of the best statistics that we have come from Dr. Halbrecht of Israel, and it is interesting that in one of his reported series of 130 patients he observed that only 8 cases were of the exudative form and the other 122 were of the latent form -in other words, tuberculosis diagnosed by endometrial biopsy, intrauterine washings and culture, or examination of portion of tubes removed incidental to ectopic pregnancy or tuboplasty. So, using his figure, the latent form exists perhaps fifteen times as often as the exudative form. If you wish to take the series of 19 cases reported by Dr. Schaupp, you might jump to the conclusion that another 285 were missed. That is probably not valid because most of the patients would never go to the hospital.

Another recorded series was reported by Halbrecht on 1,550 consecutive endometrial biopsies in patients whose only complaint was sterility. He picked up an incidence of tuberculosis of 4.58 per cent, and in those patients with tubal occlusion he demonstrated the incidence of tuberculosis was 40.6 per cent. Now again these statistics cannot be applied to our situation directly, for in Israel the incidence of gonorrhea is extremely rare.

Those of you who deal with charity practice in the teaching institutions and county hospitals are apt to find a higher incidence of tubal occlusion due to gonorrhea. Those of us who deal largely with private patients, who either have not had gonorrhea or, if they have had it, have had adequate therapy early, will find a higher incidence of tuberculosis.

Dr. William M. Wilson, Portland, Oregon. I was requested to participate in a brief dis-



Fig. 1. High power magnification of calcified (psammoma) bodies in the submucosa, mucosa, and lumen of the ampullar portion of the Fallopian tube. (From Wilson, William M.: West J. Surg. 41: 614, 1933.)

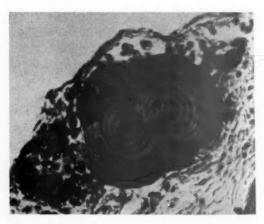


Fig. 2. High power magnification of calcified (psammoma) bodies in the subserosa of the Fallopian tube. Note the partial fusion of the two large bodies in the center. (From Wilson, William M.: West. J. Surg. 41: 614, 1933.)

cussion of this interesting paper and, accordingly, looked up the incidence of pelvic tuberculosis in three of our major hospitals in Portland. S. Vincent's Hospital has only 2 cases on record since 1946. At Providence Hospital there were also, only 2 cases on record since 1946. The records at Emanuel Hospital contain 18 cases since 1932. Eleven of these occurred in the last 14 years, during which time the incidence of tuberculosis in general has markedly decreased in our community.

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I do have a couple of interesting pictures, however, of a Fallopian tube which contained su face tubercles grossly resembling those seen in pelvic tuberculosis. In 1928, Dr. Warren Hinter, Professor of Pathology, University of Oregon Medical School, presented these pictures, Figs. 1 and 2, with the comment that he was unable to make a diagnosis. I had never seen a bizarre microscopic picture such as this, and with his permission, submitted them to several eminent pathologists including Dr. Emil Novak of Baltimore and Dr. A. S. Warthin of Michigan. Dr. Warthin was the only one who claimed to have any familiarity with this histological picture. He replied as follows: "The two sections from your case No. 15390 present numerous calcareous concretions of the laminated type resembling the sand bodies of the meninges. On a small scale, these are not uncommon. Nearly every tube of an old salpingitis shows some of these bodies. I have never seen one with as many as this case shows, but I see no other explanation. I think they are simply calcified hyaline concretions, arising from inflammatory exudate or dead cells, or possibly following an ectopic gestation. Similar sand-bodies are very common in papilliferous cystadenomas and cystocarcinomas of the ovary, but there is no evidence here of any malignancy or neoplasm."

Following the receipt of this letter I searched the literature and discovered that Virchow in 1863 coined the term "psammoma body" to describe sandlike particles in benign connective tissue tumors of the meninges. I also found that Horalek of Prague, in 1928, described these calcium concretions in the adnexa and regarded them as important evidence of previous tuberculosis. A little later Denton and Dalldorf of Brooklyn published an article in Surgery, Gynecology and Obstetrics, April, 1930, entitled "Pseudotuberculous Salpingitis," in which they discussed the finding of ringlike calcium deposits in 34 specimens from a total of 78 cases previously diagnosed tuberculous salpingitis. They had reviewed the clinical records as well as the specimens and concluded that the calcium bodies were probably not a natural product of a tuberculous inflammatory process, since they were absent in the more typically tuberculous lesions. I reviewed the microscopic sections of 40 cases of bonafide tuberculous salpingitis and found the same to be true.

The point I want to emphasize is that tubercles on the surface and elsewhere in Fallopian tubes, although grossly resembling tuberculosis, are not infrequently the result of calcium deposits like those described above, which probably have no relation to present or past tuberculosis.

Studies of the isolated perfused human placenta

I. Methods and organ responses

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ALAN J. MARGOLIS, M.D.
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PROGRESS in understanding the functional aspects of the human placenta is understandably slow because the organ is relatively inaccessible prior to delivery. Many of the elegant techniques evolved for studying the functions of the kidney, heart, liver, or lungs are not feasible or safe in the pregnant subject. There are certain advantages, therefore, in the study of the surviving human placenta in vivo, but there are also many limitations.

A number of investigators have utilized the isolated perfused fetal circulation of the placenta for a variety of purposes. In many instances, the primary purpose has been to study the pharmacologic reactions of the fetal vascular bed or of the umbilical vessels. ¹⁻⁴ Nyberg and Westin ⁵ were the first to report the use of heparinized human blood, and they estimated the oxygen consumption of the intact, term placenta to be

3.7 ± 0.9 ml. per kilogram per minute. They observed vasoconstriction from increased oxygen concentration and vasodilatation in the presence of hypoxia. Chesley⁶ perfused an individual cotyledon in a Lindbergh-Carrel pump primarily for the purpose of detecting the elaboration of toxic or antidiuretic materials. Pincus,7 Romanoff,8 Troen and Gordon,9 and Troen10 have chiefly concerned themselves with the production of steroids, whereas, Krantz and Panos¹¹ have designed a double perfusion apparatus which is intended for the study of placental transfer. In all but the last instance, the perfusions have been nonpulsatile with high pressures or low rates of flow, and with perfusion of the fetal circulation only.

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A suitable preparation can be used advantageously for the following purposes: (1) Products synthesized by the placenta can be isolated and identified, thus avoiding confusion about their sites of origin. It must be shown, however, that the quantities recovered in perfusates exceed those which can be extracted from the fresh organ. (2) During synthesis, products can be labeled with radioactive isotopes which are not safe to use on the intact human subject. (3) The organ may be exposed to specific enzymatic poisons, to drugs, or to periods of several hypoxia to assist in the elucidation of is metabolic activities. For these purpose.

From the Department of Obstetrics and Gynecology, University of California School of Medicine.

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Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. lev

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he wever, isolated pieces of placental tissue or specific extracts are frequently superior. (4) The metabolism of the intact organ can be readily studied. (5) Finally, it might be he ped that the isolated and doubly perfused organ might be utilized as a model for the study of the placental transfer of gases and foodstuffs, but over a period of 5 years we have not been able to achieve the proper conditions necessary to accomplish this goal. The difficulties have been twofold: (a) our inability to duplicate the in vivo circulation of the intervillous spaces without injury to the villi, and (b) increases of capillary permeability, which were probably due to insufficient amounts of specific serum globulins in our perfusion fluids. The latter difficulty could be obviated if one had an inexhaustible supply of intact human plasma.

The perfusion apparatus

The primary design of the apparatus was based upon that described for the perfusion of rabbit livers by Young, Prudden, and Stirman.¹² When the placenta is being used for a study of its synthetic products, it is convenient to combine the perfusates emerging from the maternal surface and from the fetal circulation in a single "lung" for oxygenation. The circuit employed for this purpose is shown in Fig. 1. For transfer studies, a duplicate gassing chamber may readily be installed and the 2 circulations kept separate.

The mechanical heart is a latex finger cot driven by an air piston which has an adjustable stroke volume and stroke rate. The unidirectional flow is maintained by a pair of glass ball valves. The systolic and diastolic pressures are recorded proximally to the p int of entry through the 2 umbilical atteries. The bubble trap contains a Van Sike thermometer. The flow meter is a simple chamber containing 2 electrodes so spaced that the distance between the points corresponds to an exact volume of 30 ml. When the flow is shunted through this meter by occluding the "vein" distal to the meter with a solenoid valve, the time for filling the chamber is automatically recorded. If

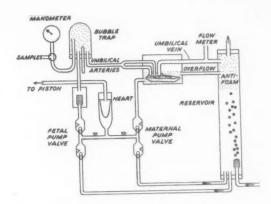


Fig. 1. Schematic diagram of the circuit as arranged for combined fetal and maternal perfusates.

the pressure on the arterial side should fall below 20 mm. Hg or rise above 200 mm. Hg (indicating some mechanical failure), an electronic device shuts off the pump. The venous return goes into a plastic chamber through which the gas mixture flows. The 95 per cent oxygen and 5 per cent carbon dioxide mixture is prewarmed and enters the "lung" through fritted glass funnels. It is necessary to utilize a small quantity of Dow antifoam at the top of the chamber to prevent foaming. Although the antifoam, a strong surface active agent, is sparingly soluble, it may well affect membrane permeability. T-tubes are inserted at various points so that samples may be withdrawn or glucose may be infused continuously without opening the door of the surrounding box.

The entire circuit is contained in an airconditioned cabinet maintained at 37° C. and 90 per cent humidity by means of a

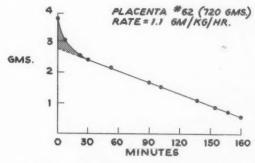


Fig. 2. Rate of disappearance of glucose from the perfusate.

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motor-driven fan, heater element, and humidifier. A sliding Plexiglas door permits frequent observation or access.

Preparation of the placenta

Placentas delivered vaginally were found to be heavily contaminated with bacteria and frequently lacerated; so studies were limited to those placentas delivered at the time of elective cesarean sections. With the use of an aseptic technique, the placenta was rinsed with warm saline solution, membranes were trimmed, and the umbilical cord was cut 1 inch from its insertion. The 2 umbilical arteries were mechanically dilated with tapered glass rods and plastic intravenous tubing was introduced into each artery and threaded past the cord to the fetal surface. Avoidance of the thick-walled umbilical arteries is absolutely essential for the achievement of high flow rates. A cannula was inserted into the vein which was then tied in place. The fetal circulation was then washed free of blood with warm Krebs-Ringer bicarbonate solution containing heparin, using a gravity flow with a pressure of 60 mm. Hg. The maternal surface was then placed upon a perforated plastic plate in a sterile basin. The basin was perforated with tubes on either side so that perfusion fluid could flow continuously over the decidual plate. On several occasions, multiple tubes were placed through the decidual plate into the intervillous space but in our hands this resulted

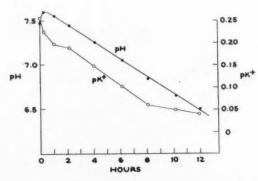


Fig. 3. Changes in the concentrations of hydrogen and potassium ions.

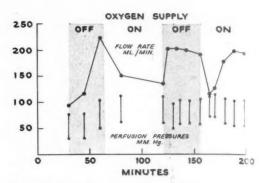


Fig. 4. Response of the fetal vascular bed to low and high oxygen concentrations.

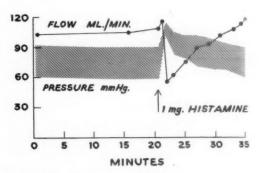


Fig. 5. Response of the fetal vascular bed to histamine.

in injury to the fetal capillaries. Every effort was made to begin the actual perfusion within 30 minutes after delivery.

Perfusion fluids

The earliest perfusions were attempted with defibrinated, heparinized fetal cord blood. In each instance, obstruction of the fetal capillaries occurred within an hour. The obstruction may have been caused by cell sludging and appeared to be in the post-capillary limb, inasmuch as the rate of transfer of water from the fetal to the maternal circulation increased markedly. The difficulty was not due to ABO incompatibility or to gross clotting, but might have resulted from residual fibrinogen. The preliminary report by Krantz and Panos¹¹ indicates that success with whole blood may be achieved by pretreatment of the blood with fibrinolysis.

In any event, calculations revealed that red blood cells or hemoglobin were not 19/1

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e ential for adequate oxygenation. The extrapolation of oxygen utilization data from Warburg experiments indicates an oxygen requirement of 3.5 ml. per minute per kilogram, which is very close to the direct observations made by Nyberg and Westin.5 The solubility of oxygen in Ringer's solution at 37° C. is 23.8 ml. per liter, so that a flow rate of 74 ml. per minute would supply an adequate quantity for a 500 gram organ. Flow rates were usually several times this minimal requirement.

The perfusion fluid which was finally adopted had the following constitution: Each liter contained 80 ml. of the commercial tissue culture medium (Mixture 199)* described by Morgan, Morton, and Parker, 13 but did not contain bicarbonate; 50 Gm. of human albumin (which contained 1.2 per cent sodium chloride by weight)†; 0.8 Gm. of additional glucose; 75 mg. each of penicillin and streptomycin; and supplementary electrolytes sufficient to bring the final concentrations to the following composition (in milliequivalents per liter): Na 152, K 5.9, Ca 5.9, Mg 2.3, Cl 103, and total PO₄ 1.4. The human albumin is needed for the maintenance of oncotic pressure and for the transport of steroids.

Despite the antibiotics, colonies of aerogenes bacteria could be cultured from the medium in many instances after 8 to 12 hours.

Metabolic factors

One of the parameters of viability was the rate of glucose utilization. For any given organ, this was remarkably constant, and showed no signs of decreasing for at least 12 hours, which was the usual limit of perf sion time. Fig. 2 illustrates the rate of d sappearance of glucose from the perfusate in a typical experiment. The shaded area of the curve is due to the movement of glacose into the intracellular compartment of the placenta which, in this instance,

amounted to 56 per cent of the organ weight. The average rate of glucose utilization is 1 Gm. per Kg, wet weight per hour. Troen and Gordon⁹ showed that citrate utilization is about one tenth of this value.

The metabolism of the placenta results in the production of organic acids. This, or possibly the release of intracellular hydrogen ions, causes a steady fall in the pH of the perfusate. This is accompanied by a nearly parallel rise in the potassium ion concentration of the perfusing medium (or fall in the pK+) as illustrated in Fig. 3. During this experiment, no adjustments were made, but it is ordinarily necessary to adjust the pH hourly by the addition of sodium bicarbonate.

When bilirubin was introduced into the fetal circuit, there was a slow but definite transfer to the maternal circuit in every instance. The absolute rates varied from one organ to another and are probably meaningless in terms of the in vivo situation. The important observation was the complete absence of any conjugation with glucuronic acid (i.e., formation of the soluble or direct bilirubin). Neither the fetus nor the placenta appears to possess this capability.

Response of the fetal circulation to variations of oxygen and selected drugs

The typical response of the fetal vascular bed to hypoxia or to high oxygen is shown in Fig. 4. In this instance the placenta weighed 488 grams, the perfusion medium contained 0.2 per cent fetal serum in place of the human albumin, and the stroke rate was 120 per minute throughout. The apparatus is so designed that vasoconstriction produces both a rise in the systolic and diastolic pressures and a decrease in the flow rate. It can be seen that hypoxia results in vasodilatation and high oxygen produces transient vasoconstriction.

There is indirect evidence that the fetal vascular bed of the placenta behaves in a similar fashion in utero. After studying the effects of oxygen administered to pregnant women at term, Prystowsky14 concludes: "In the normal parturients who received oxygen

^{*}Obtained from Microbiological Associates, Inc., 4846 Be hesda Ave., Washington 14, D. C.

Donated by Cutter Laboratories, Berkeley, California.

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there was a rise in pO₂ on the maternal and fetal sides, but the latter to a lesser degree. In other words, what the fetus apparently does is decrease the size of the capillary bed, so that he gets what he wants at the pressures he desires. These findings are not at all surprising, for one would expect that the fetus in utero would have some means of expanding and contracting his exposed capillary bed."

The fetal vessels respond to minute doses of histamine or serotonin by vigorous contraction, but we were unable to confirm earlier reports about a response to epinephrine and norepinephrine. The response to the injection of 1 mg. of histamine into the fetal circuit is illustrated in Fig. 5. In this experiment, the organ weight was 848 grams, the volume of perfusion fluid on the fetal side was 750 ml., the pH was 7.8, and the pulse rate was constant at 120 per minute. On occasions, the placenta would lose its responsiveness to serotonin or histamine while maintaining its normal glucose utilization.

The problem of viability or functional integrity, therefore, is complex and can be answered only with respect to each individual function in question.

Summary

Methods of perfusing the isolated, surviving human placenta under nearly physologic circumstances are presented. During periods up to 12 hours, the rate of glucose utilization is about 1 Gm. per kilogram per hour. The production of organic acids causes a steady rise in hydrogen ion concentration with a parallel rise in potassium concentration. No conjugation of bilirubin with glucuronic acid could be observed.

Hypoxia results in vasodilatation with increased rates of flow through the fetal vascular bed, whereas high oxygen pressures cause the reverse. It is believed that similar responses occur in utero. The fetal circulation is not responsive to epinephrine or norepinephrine but responds with vigorous vasoconstriction to serotonin and histamine.

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Studies of the isolated perfused human placenta

II. Progesterone content of perfusates

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It has been known for almost 30 years that the human placenta contains compounds which have gestogenic effects. Ample confirmation of this observation, including the isolation and identification of progesterone, has appeared in the literature since that time. More recently, Zander and associates have extracted Δ 4-3-ketopregnene-20-alpha-ol and Δ 4-3-ketopregnene-20-beta-ol from placenta and have shown that these compounds are active progestational hormones.

The evidence, recently reviewed by Zander, ¹⁴ that the placenta produces progesterone, although indirect, is convincing. In addition to evidence such as the maintenance of elevated plasma progesterone and/or urinary pregnanediol levels during pregnancy in the absence of the corpus luteum, adrenals, or fetus, experimental data

are also available which indicate that the enzymes required for the synthesis of progesterone from some precursors are present in the placenta. It has been shown, for example, in placental perfusion experiments that cholesterol and Δ 5-pregnenolone can be converted to progesterone and in incubated placental tissue that Δ 5-pregnenolone may be converted to progesterone. The following studies, which have been carried out as part of a broad program in the study of placental function, lend additional support to the concept that the placenta is capable of synthesizing progesterone.

Methods

Six term placentas obtained at cesarean section were perfused for 2 to 12 hours by the technique of Goerke and associates. 18 Aliquots (200 ml.) of the perfusate, to which was added 5,000 c.p.m. of progesterone 4-C14, were analyzed by a modification of the method of Zander and Simmer. 19 The aliquot was adjusted to pH 12 to 13 by the addition of one-third normal sodium hydroxide and extracted 3 times with 3 volumes of ether; ethyl acetate (1:1, V/V) with readjustment of the pH between extractions. The combined extracts were evaporated to dryness and the residue taken up in 70 per cent methanol. Lipids were removed by solvent partition and cooling and the final residue chromatographed in the

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Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960.

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Table I

No.	Placental weight (grams)	Length of perfusion (hours)	Volume of perfusate (ml.)	Progesterone content of perfusate (µg)	Progesterone p unit weight o placenta (µg per gram
71	430	2	2,250	3,243	7.60
86	887	12	1,675	4,750	5.35
87	550	11.75	1,860	7,650	13.91
93	494	12	1,690	210	0.43
94	440	9.5	1,770	3,560	8.10
95	583	8.0	1,980	5,940	10.18

heptane-formamid system. The area with an Rf value corresponding to that of authentic progesterone was eluted and rechromatographed in the heptane-methanol-water (70:30) system. The area containing progesterone was eluted and the ultraviolet absorption was estimated at 240 mu and corrected for the paper blank. The eluate was then divided and the samples prepared for counting in a liquid scintillation spectrometer and for the development of sulfuric acid chromatogens. In all samples, the ultraviolet absorption and sulfuric acid chromagen patterns were identical to those of progesterone. Correction for losses during the procedure was made according to the recovery of progesterone 4-C14.

Results

Corrected values for the progesterone content of placental perfusates appear in Table I. In order to be able to compare the progesterone content of placental perfusates to previously reported values for the placental content of progesterone, the effect of perfusing fluid on the extraction of progesterone from a fresh placenta was studied in 2 experiments. The progesterone content of placental tissue, homogenized for 30 minutes with a 200 ml. aliquot of the perfusing fluid in a Waring Blendor, was compared to the content of an equal aliquot of the same placenta extracted directly. No significant difference was found in the extraction of progesterone by the two methods.

One millicurie of acetate-C¹⁴ was added to the perfusing fluid at the beginning of the perfusion of placenta No. 71 and progesterone-16H³ was used as the tracer. No incorporation of C¹⁴ into progesterone or Δ 4-3-ketopregnene-20-ol was found.

Comment

Large amounts of progesterone were recovered from 5 of the 6 perfusates. With respect to the nonproductive placenta (No. 93), examination of other data regarding glucose utilization and chorionic gonadotrophin production in this experiment indicates that its function in these respects was similar to that of other placentas which were perfused. For this reason, it has been included for statistical purposes.

Zander,14 in a series of 13 term placentas, found 1.95 (S.D. \pm 0.55) μg of progesterone per gram of placenta. The placental perfusates, however, contained a mean of 7.6 (S.D. \pm 4.5) μ g of progesterone per gram of placenta. The means of the 2 groups of data remain significantly different (P > 0.01). This difference suggests either that perfusing fluid is a more efficient means of extracting progesterone produced and/or stored in the placenta or that the perfused placenta is able to synthesize progesterone. The preliminary studies indicate that the recovery of progesterone from placenta is not significantly different in the presence of perfusing medium. Therefore, it would appear that the excess of progesterone over that which can be extracted from the term placenta represents net synthesis.

Summary

After 6 full-term placentas were perfued from 2 to 12 hours, the progesterone content

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fu ed nt nt of the perfusates was greater than could be ac ounted for by simple extraction of preformed steroid. It is suggested that the excess re resents progesterone synthesized during pe fusion.

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Discussion

Dr. Ervin E. Nichols, Pasadena, California. I should like to ask Dr. Page a question that has been asked me, and for which I have not been able to find an authoritative answer. The people from our diabetic group have asked about insulin going across the placental barrier. I wonder if Dr. Page could give us some light on this particular problem.

Dr. Page (Closing). To answer Dr. Nichols' question, we have not had an opportunity to Gregory, editor: Recent Progress in Hormone Research, New York, 1957, Academic Press, Inc., vol. 13, p. 379.

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perfuse an intact, gravid uterus. The technical difficulties would be great and I do not know whether anyone has attempted this. Dr. Assali and others, working in Sweden, have perfused human fetuses and have kept them alive for many hours.

I have no direct experience with insulin transfer. From the literature, I gather that insulin is not transferred across the human placenta in physiologically significant quantities.

Serum lipids in pre-eclampsia-eclampsia

RUSSELL R. DE ALVAREZ, M.D. GLORIA E. BRATVOLD, B.S.*

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RECENT interest in the production of arteriolar vascular constriction and of hypertension has raised the question of the possible influence of hypercholesterolosis and other lipid changes1-3 on the pathogenesis or even the causation of toxemia of pregnancy. Interest in the relationship of elevated serum lipids was generated through the study of diseases in which cholesterol deposition in vessels of the circulatory system was shown to have occurred. In some types of chronic hypertensive vascular disease, diabetes, and nephritis, evidences of atheromatous deposition in vessels have been demonstrated. Even though Zeek and Assali4 described obstructive changes in decidual vessels of patients with pre-eclampsia, due to acute atherosis of spiral arterioles and venous lakes, no consistent lipoid deposition has been substantiated and the serum lipid levels have not been related to such events. It is well known⁵ that an increase in circulating lipids occurs in normal pregnancy and that this rise is a progressive one as pregnancy ad-

vances. During early pregnancy, the values for total cholesterol, ester cholesterol, free cholesterol, lipid phosphorus, and phospholipids, as well as total lipids, do not differ significantly from those found in normal nonpregnant controls.⁶ All values increase as pregnancy approaches term with a return to normal of most fractions by the sixth postpartum week, with the exception of total lipids and lipoproteins.

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Relatively few reports of lipid metabolism during pregnancy pertain to the patient with toxemia of pregnancy; most investigations are limited to normal pregnancy. When comparisons are made of values in patients with pre-eclampsia, the evaluation is made in terms of the results obtained from nonpregnant patients. Such comparisons are not really valid because of the rise which is known to occur in normal pregnancy. Thus, in order to assess the significance of values in toxemia of pregnancy at a given duration of pregnancy, it is necessary that comparisons of findings in pre-eclampsia-eclampsia be made with those known to occur in normal pregnancy at that given duration of preg-

After we determined the pattern during normal pregnancy⁶ in our own laboratory, it became possible to compare values obtained in toxemia of pregnancy or in any other complication of pregnancy at identical durations of pregnancy and to render a critical and statistical appraisal of any differences.

Vasoconstriction plays an important role in most instances of pre-eclampsia-eclampsia

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but the explanation for its causation is not env. Inasmuch as arteriolar vascular constriction due to hypertension in the nonpregnant patient has been related to hyperci olesterolosis and since hypercholesterolemia and other lipemias occur and increase as pregnancy advances, the present work was undertaken to study possible relationships between lipogenesis and eclamptogenesis.

Materials and methods

Fifty-three patients with toxemia of pregnancy comprised the group in whom the various lipid measurements were studied. The diagnosis of mild pre-eclampsia was made in 32 patients; in 16 a diagnosis of severe pre-eclampsia was made. In 5 additional patients the diagnosis of eclampsia associated with convulsions and coma was made. Most had had little or no prenatal care, assumed an attitude of indifference, came from a low socioeconomic stratum, and usually were of higher parity, differing thus from our normal pregnant and the nonpregnant control series.

The total study comprised 274 determinations performed in the over-all group of toxemia patients. Where possible, the same determinations of each lipid fraction were carried out in the antepartum period and repeated during the early and late puerperium. In none of the patients with mild pre-eclampsia was it possible to obtain samples at the sixth week post partum; however, it was possible at that time to study the group with severe pre-eclampsia and eclampsia.

In each patient determinations of total lipids, total cholesterol, ester cholesterol, free cholesterol, and phospholipids were made. The method was the same as that presented in detail in our earlier publication.6 It is important to note that all patients in this series were hospitalized. The collection of specimens was uniform and adhered to the same standards established for the normal promancy group. Statistical treatment of the dan included calculation of the mean, standard deviation, standard error of the mean, and probability. All the toxemias of

pregnancy reported in this study occurred as complications of the third trimester of pregnancy. In order to make the data from the normal pregnant control group of patients comparable to those of the preeclampsia-eclampsia group, the data of the normal pregnant group were assembled into a third trimester of pregnancy group for comparative statistical analysis. It was determined that the values obtained at any one of the various stages in the last trimester of the antepartum period of normal pregnancy revealed no significant differences from any other subdivisions during the same period. Therefore, all data for the normal pregnant control group, twenty-ninth to the fortieth week of pregnancy, were considered as a single antepartum unit and compared with data derived from the study of those patients developing antepartum pre-eclampsia or eclampsia at the same period of gestation. The number of patients with eclampsia was too small to be considered as a separate statistical group; hence, the data for the with severe pre-eclampsia eclampsia were combined. With this exception, statistical methods were carried out as in our earlier publication.

Since all the mild pre-eclampsia during the antepartum period occurred between the thirty-fifth and thirty-seventh weeks of gestation, the mean data for this group are represented as occurring at the thirtyseventh week to permit a convenient comparison of results without sacrificing accuracy. Most of the antepartum determinations in patients with severe pre-eclampsia and eclampsia were obtained between the thirty-fifth and fortieth weeks of gestation. These mean values also are grouped together and appear on the illustrations at the thirtyseventh week. In others, severe degrees of pre-eclampsia and eclampsia occurred earlier than the thirty-fifth week and are individually depicted.

Results

Total lipids. In 7 normal pregnant patients, the average value for total lipids during the last 4 weeks of normal pregnancy

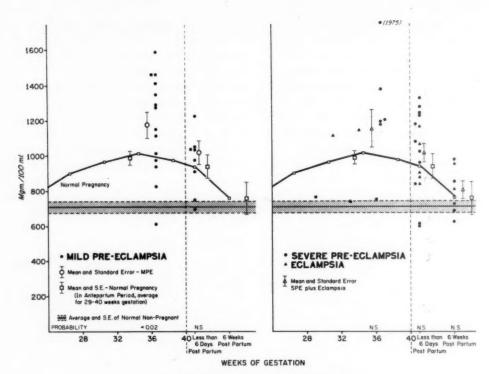


Fig. 1. Serum total lipids (toxemia).

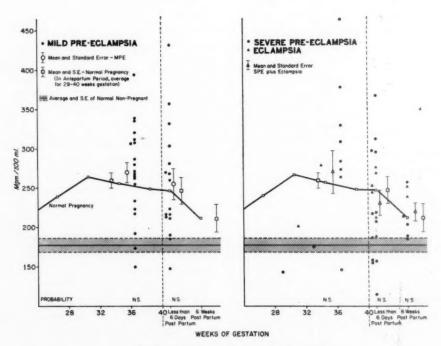


Fig. 2. Serum total cholesterol (toxemia).

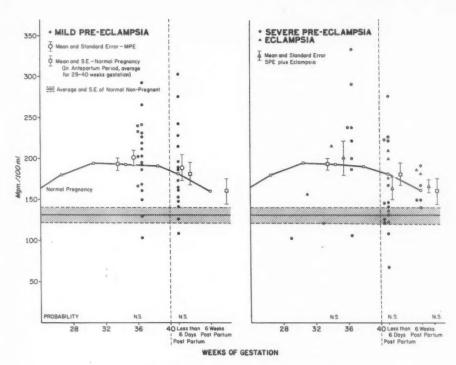


Fig. 3. Serum ester cholesterol (toxemia).

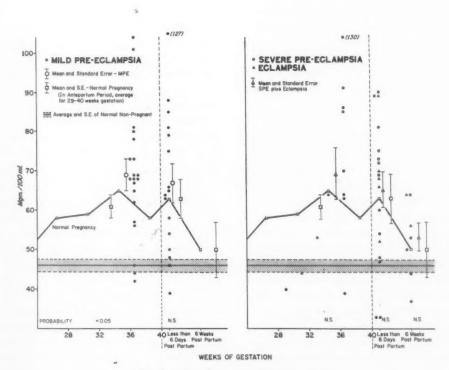


Fig. 4. Serum free cholesterol (toxemia).

was: mean 974 mg. per milliliter of serum; standard deviation, 154; probability 0.001; per cent of normal nonpregnant control, 137. A wide range of values for total lipids occurred (Fig. 1) in the group of patients exhibiting mild pre-eclampsia in the antepartum period. Nevertheless, the mean value for mild pre-eclampsia is significantly elevated (P = < 0.02) above the average value obtained in normal pregnant patients in the third trimester. However, the range of determinations in the postpartum period closely resembled that of normal pregnancy, with no significant difference being observed. In severe pre-eclampsia values for total lipids seem higher than in normal pregnancy but, when grouped, the mean for severe toxemia, although almost 200 mg. per cent above the mean of the normal pregnant level, showed a relatively large standard error. The mean for severe pre-eclampsia and eclampsia, therefore, was not statistically significantly elevated above the value for normal pregnancy. This was probably brought about because of the presence of quite low values in 3 patients at the twentyninth, thirty-third, and thirty-fourth weeks, respectively. On the other hand, the total lipids in 2 patients with antepartum eclampsia were almost 200 mg. higher than the value for normal pregnancy of the same duration. The distribution of the postpartum values is similar to that for normal pregnancy; there was no statistically significant difference. One patient with severe preeclampsia exhibited a very high total lipid value of 1,975 mg. per cent in the antepartum period and persisted at high levels but somewhat less than prior to delivery; the value during the postpartum period was 1,324 mg. per cent. The other lipid fractions in this patient also were comparatively higher than those of others in the group.

Total cholesterol. The values obtained for total serum cholesterol are illustrated in Fig. 2. While the mean value in mild pre-eclampsia reveals an elevated trend in the antepartum (value) and early postpartum (value) periods, statistical analysis shows no significant difference from the mean for

normal pregnancy. In the severe toxemia, several patients exhibited low values early in the third trimester and in the immedia puerperium. The low values persisted in the same patients who exhibited lower values in the antepartum period. At the sixth week post partum, the mean for severe pre-eclampsia-eclampsia had decreased but still had not yet returned to limits noted in the normal nonpregnancy group.

Ester cholesterol. The values of ester cholesterol in toxemia followed a pattern similar to that of total cholesterol and is depicted in Fig. 3. The findings in toxemia of pregnancy showed no statistical difference when compared to those of normal pregnancy.

Free cholesterol. Most of the individual observations of free cholesterol in mild preeclampsia (Fig. 4) are above the mean for normal pregnancy; the difference between the means for the two groups is only statistically significant at the 0.05 level in the antepartum period. In severe pre-eclampsia and eclampsia the general pattern of free cholesterol is similar to that of ester cholesterol. Even though the trend in severe toxemia seems elevated above that of normal pregnancy, the differences in the antepartum values are not statistically different. The elevation persisted during the first week post partum but the difference was not statistically significant.

Lipid phosphorus. The antepartum mean for serum lipid phosphorus and phospholipids (Fig. 5) follows an elevated trend in all types of toxemia, but the differences are not statistically significant. The postpartum values in mild pre-eclampsia also are not statistically different from those in the normal pregnancy group. In severe pre-eclampsia-eclampsia they are significantly reduced in the early and late puerperium.

Comment

The diet constitutes the principal, if not the only, source of lipids for metabolis n. The initial transport from the gastroint stinal tract is by way of the lymphatics to the systemic circulation where they are trans-

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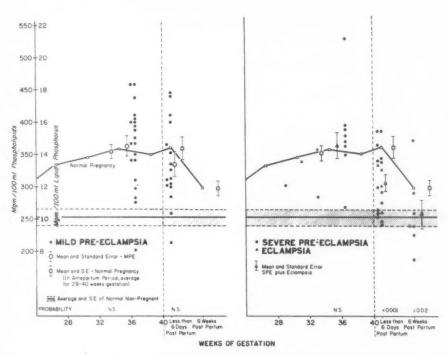


Fig. 5. Serum phospholipids and lipid phophorus (toxemia).

ported to the liver and the fat depots. Lipids may shift from the liver to the circulation and vice versa. The cholesterol esters probably are as important in the metabolism of lipids as are the phospholipids. Most of the metabolic changes of lipids are thought to occur principally in the liver rather than in the blood stream proper. In some types of severe pre-eclampsia and eclampsia the liver is often seriously affected and should theoretically interfere with lipid metabolism. While there are morphologic evidences of this in isolated instances of severe degrees of toxemia of pregnancy, in our group we have not been able to show a statistical difference in the severe toxemia group from those noted in the normal pregnency group. Perhaps comparison of the means of the isolated fractions is not as maningful as a comparison of the ratio of clolesterol to phospholipid. It may well be that the C/P ratio, if maintained in the ci culation, is the determining regulatory mechanism especially since, in our patients, an elevation of one fraction was usually associated with an elevation in every other lipid fraction. The ratio of total cholesterol to phospholipid in normal pregnancy at 37 to 40 weeks did not differ significantly from that in the normal nonpregnant patient. However, the C/P ratio in all toxemias of pregnancy was significantly elevated, with the highest level occurring in the severe pre-eclampsia-eclampsia group.

Even though the serum lipids in toxemia of pregnancy showed an apparently slightly accentuated trend, analysis of our data showed no statistically significant differences when compared with those of normal pregnancy at the same week of gestation. Also, the phospholipid levels, while showing an increase, were not markedly elevated compared with that in the normal pregnant group. However, the postpartum values in the severe pre-eclampsia-eclampsia group were significantly lower than in the normal pregnant group, indicating that a mechanism is probably operating to produce a rapid breakdown or rapid excretion of this fraction.

Table I. Cholesterol/phospholipid ratio in normal and toxemia pregnancy

Ratio	Duration of pregnancy	Normal pregnancy	Mild pre-eclampsia	Severe pre-eclampsia	All toxemia
Total C/P	37-40 weeks	0.711	0.742	0.823	0.749
	1-6 days post partum	0.686	0.760	0.717	0.746

The increase in serum lipids during pregnancy is probably related to the simultaneous increase of endogenous estrogen. Entenman and co-workers7, 8 noted this in experimental animals following the administration of pregnant mare's serum, but following the administration of estrone there was a doubling of the blood lipids with an increase of all fractions; the most prominent increase was in the neutral fat. Estrone, estradiol, ethinyl estradiol, and stilbestrol all produced increases in the total fatty acids, phospholipids, and cholesterol of the blood.9, 10 With use of P32, diethylstilbestrol was shown¹¹ to stimulate the rate of synthesis and the turnover of blood phospholipids. Stammler¹² reported the development of hyperlipemia followed by atherosclerosis when chicks were implanted with 25 mg. of stilbestrol. Adlersberg13 noted an average increase of 15 per cent in blood cholesterol and 26 per cent in phospholipids with the decrease of 51 per cent in neutral fat in the blood of patients receiving cortisone. This study on humans tends to verify the studies in rats where an increase in total and ester cholesterol and phospholipids occurred after the administration of cortisone. Estrogen administration results in an increased plasma cortisol concentration without a simultaneous increase in the urinary metabolites of cortisol. In our studies of the urinary excretion of the 17-hydroxycorticosteroids we have noted no significant increase in excretion in patients with toxemia of pregnancy. This finding might well be explained on the basis of a diminished rate of metabolism of cortisol to metabolites with a greater retention of cortisol in the circulation.

It would seem that the elevation of the estrogen titer is one of the principal con-

tributors to the lipemia in pregnancy. Prolably the principal function of the lipemia of normal pregnancy is to provide an energy reservoir of lipids for the developing fetus. In toxemia of pregnancy it is conceivable that energy transferred to the fetus is not fully accomplished and that the lipids are consequently deposited in the characteristic placental infarcts of pregnancy toxemia, thus accounting for the fact that these products are not permitted to accumulate in the maternal circulation of the pre-eclamptic patient in a greater concentration than that found in the normal pregnant patient.

Conclusions

1. A significant rise in total lipids and all other fractions occurs during normal pregnancy, compared with values in the normal nonpregnant state or with those in early normal pregnancy.

2. The hyperlipemia in pre-eclampsia-eclampsia is statistically equivalent to that found in late normal pregnancy. The individual serum lipid fractions in the toxemias of late pregnancy are not élevated when compared with the values in the last half of normal pregnancy. A rise in C/P ratio does occur in all true toxemias of pregnancy, with the greatest increase occurring in severe pre-eclampsia-eclampsia.

3. No specific chemical alteration of lipids occurs in toxemia of pregnancy.

4. Despite the fact that all lipid fractions are elevated above the normal nonpregnant level in normal pregnancy and in patients with toxemia of pregnancy, it is not possille on the basis of our study to relate these findings to any specific lipodystrophy.

5. The hyperlipemia of pregnancy sec as to be directly related to the hyperestro-

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genemia of pregnancy which may be related to the accompanying elevation of the adrenal certicoids. 6. Careful serial studies of serum lipids during normal pregnancy offer a framework for assessing the lipid processes in the abnormalities of pregnancy.

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Discussion

DR. HERBERT TRAUT, San Francisco, California. For years we have been told that degenerative areas in the placenta were associated with this, that, or another disease peculiar to pregnancy. We have practically been told that degeneration on maternal surfaces of placenta was very important at the beginning of toxemic changes in pregnancy patients. There has been nothing advanced in the last 10 to 15 years to support this thesis. As a matter of fact, with the accumulation of more experimental material, it seems less and less tenable.

Today Dr. de Alvarez has told us that the degenerative changes in the placenta were associated with so-called infarcts of the placenta. I have to say that advocates of these views are speaking in terms of theory. However beautiful these may be in biochemical or physiological terms, they just don't stand up if a person really has contact with a large obstetrical material in which one examines every single placenta that goes through, not just in terms of gross morphological changes, but those where there was any change that was observable were examined under the microscope.

Having done thousands of these examinations, I know that the villus degeneration has nothing in the world to do with toxemia of pregnancy. Certainly it does not have anything to do with chronic nephritis. I don't think it has anything

to do with the storage of unused fats in the placenta, although I'm not sure of that.

During the war years on the East Side of Manhattan there was a tremendous number of undernourished individuals. We received hundreds of placentas with enormous degenerative areas of all sorts, not only those which consisted of clotted blood largely in between the villi, but also degenerative areas of epithelium on the villi, as well as these so-called infarcts.

There is no correlation between these changes and the various clinical syndromes. On the other hand, just as soon as we got funds to supply these people with vitamins and balanced diet, the infarcts almost disappeared. We do not see these lesions in San Francisco, for the people here are well nourished. I would like very much to have seen placentas from German women in the war years, or in some of the concentration camps; I think these probably exhibited placental degeneration.

I think these lesions are related to nutrition, and in that respect I think that Dr. Russell is correct. It is, however, very hard to correlate these changes, whatever their cause may be, with the clinical experiences of a woman during her pregnancy.

Dr. Ernest W. Page, San Francisco, California. I would like to comment upon one of

Dr. de Alvarez' closing remarks which was concerned with the apparent purposes of the lipid changes in pregnancy. He remarked that the excess plasma lipids might be a major source of energy for the fetus.

I believe that it has been well demonstrated by Popjak and by others that the lipid fractions discussed in this presentation do not reach the fetus in any nutritionally significant quantities. On the other hand, Dr. Charles Van Duyne, working in our department, has recently demonstrated a rapid transfer of labeled free fatty acids to the fetus in late pregnancy in the rabbit and a slight, but definite, transfer in pregnant sheep. Based upon comparative levels of free fatty acids in the newborn, he believes that transfer rates in women are intermediate between the sheep and the rabbit.

Nevertheless, the primary source of energy for the human fetus in utero must be carbohydrate. At birth, the fetal plasma concentration of free fatty acids is very low, and it is comparable to the low level in adults achieved by high carbohydrate and low fat feedings. Dr. Van Duyne found that within a few hours after birth babies achieve adult levels of fatty acids. The fetus shifts from a carbohydrate burner to a fat burner, and this shift is apparently important for survival. In newborn sheep, for example, he found that when this rise did not occur the animals all died.

The mechanism which triggers the lipid mobilization after birth is not understood, but it may be concerned with epinephrine or nor-epinephrine release. The matter of survival, especially in premature infants, may be inti-

mately associated with this problem of lip | metabolism in the newborn.

DR. DE ALVAREZ (Closing). I am most appreciative of the kind assistance and stimultion which Dr. Traut and Dr. Page have given us to pursue some of the areas of investigation which are so in need of exploration. The work of Dr. Van Duyne and Dr. Havel represents a significant contribution to the advancement of our knowledge as to how and for what purpose lipids are transported. Whether or not the placenta uses fatty acids as its energy source has not been elucidated. Lipids exist in the intestinal lumen as triglycerides, cholesterol ester, and free cholesterol. Triglycerides are hydrolyzed by pancreatic lipase to yield a mixture of mono- and diglycerides, glycerol, and free fatty acids. Cholesterol esterase, another enzyme of the pancreatic juice, catalyzes the esterification of free cholesterol with fatty acids to form fat droplets. The fat droplets cross the intestinal mucosa as fatty acids and as glycerides. These result in the formation of phospholipid and triglyceride. The resulting lipoproteins come not only from this source but from the free cholesterol pool and from cholesterol esters from a combination of the free cholesterol pool and the fatty acids.

Careful studies in the experimental animal as well as in human reproduction are necessary to determine the exact pathway across uteroplacental vessels to determine whether the pattern is similar to those involved in intestinal transfer. Simultaneous studies of lipids of serum and of placental lipid composition are necessary before definitive mechanisms can be stated.

Pregnanediol excretion in threatened abortion

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THE early growth and development of the human embryo depends upon vascularization and oxygenation within the uterine endometrium. An abnormal ovum or an abnormal spermatozoon may result in arrested embryonic development and subsequent abortion.1 A study of the sperm or ovum prior to fertilization is not possible. In many instances aborted embryos are macerated and difficult to evaluate microscopically. Could not withdrawal of blood supply and oxygen so necessary for growth produce the same findings? The exact nature of the human blastocyst's passage from the uterine lumen through the epithelium to the submucosa has not been observed.2, 3 The exact details of vascular adaptation to the growing human embryo are unknown.

Endometrial bleeding in the nonpregnant uterus can be controlled in a high percentage of patients by hormone therapy. Withdrawal of such therapy results in uterine bleeding. For many years the role played by hormones in threatened abortion has been a controversial subject. Is the uterine vasculature so different in the pregnant and the nonpregnant human uterus? Ramsey states that our mientation toward cyclic changes in uterine

vasculature is quite false if we look upon pregnancy as an isolated event for which special and extraordinary preparation must be made.⁴ Bartelmez demonstrated that specific adaptation for pregnancy commences on day one of the menstrual cycle and forms a smooth, purposeful sequence thereafter.⁵ This orderly sequence of events, especially the growth and regression of the spiral arterioles of the endometrium, is under hormonal control.^{6, 7} Decreasing concentrations of ovarian steroids are followed by slowed circulation in the endometrium, stasis, vasoconstriction, and necrosis. This is not the proper environment for the growing embryo.

To demonstrate the effects of hormone withdrawal in early pregnancy, mice have been injected with desoxycorticosterone acetate (DCA) daily for 5 days and then had the drug withdrawn.8 Forty-eight hours after the last injection the uteri, instead of being cherry red in color, were dark purple. The mesometrial vessels appeared to end either at the uterine wall or soon after entering the wall. The myometrial vessels were buckled and broken. The embryos were ischemic, flaccid, and torn easily. The embryos then degenerated to form the classical picture of "blighted ovum." In no case did the continued use of DCA interfere with normal pregnancy.

In addition to the changes seen following the endometrial circulatory collapse in the pregnant uterus, myometrial function is also altered by ovarian steroid levels. Csapo⁹

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has demonstrated that the length of the muscle cell in the rabbit uterus can be increased from 10 mg. to 15 mg. by estrogens administered over a 7 day period. Three weeks after ovariectomy in the maternal estrus, there is an 80 per cent decrease in actinomysin concentration and maximum tension. Treatment with estrogens reverses this change. Csapo has also shown that progesterone exhibits certain effects on myometrial function by: (1) shortening the contraction cycle, (2) lowering the ionic gradient across the cell membrane, (3) altering conduction patterns, and (4) desensitizing the myometrium to calcium lack. Some of these actions can be traced to an increased sodium and decreased potassium content of the myometrial cell.

With the assumption that hormones may exert a profound influence on the developing embryo and the uterus, it would be of value to determine by some reasonably easy, inexpensive, and accurate test how far the hormone imbalance had progressed early in pregnancy. The test could be performed at the first signs of threatened abortion or soon after the first missed menstrual period in patients who have had repeated abortions.

Much work has been done on the value of pregnanediol excretion levels in threatened abortions. Guterman has studied progesterone metabolism for many years and has added greatly to our fund of knowledge. 10 In 1939 Browne, Henry, and Venning¹¹ reported eventual abortion with diminished pregnanediol excretions. Bender12 using a Guterman test on 100 c.c. of morning urine reported that patients with low levels of urinary pregnanediol could be treated and the salvage rate increased. Randall13 also concluded that, in the presence of the low progesterone levels, as estimated from the vaginal smear, treatment might increase the salvage rate. An abortion rate of 87 per cent in those with low pregnanediol excretion was reported by Borglin¹⁴ in 1956.

Much of the earlier evaluation of pregnanediol excretion in threatened abortions was done when less accurate methods were available for pregnanediol estimation. Baker¹⁵ in 1955 reported that pregnanedial levels in threatened abortion did not accurately forecast the need for treatment or the prognosis. This conclusion was made on the basis of 57 cases studied by 12 hour urine specimens with the use of a modified Guterman test. The result of this estimation was doubled to obtain the 24 hour excretion level. Wray and Russell¹⁶ have reported the inaccuracies of estimating 24 hour pregnanedial excretion by this method.

The pregnanediol levels in some reported series have been of prognostic importance. Goldzieher and Benigno¹⁷ summarized previous series and reported a 90.7 per cent abortion rate in the low pregnanediol group. These estimations were made by older methods of determining pregnanediol excretion. In the light of our present knowledge, modern methods used today would afford us more accurate results.

This study was undertaken to evaluate the 24 hour urinary pregnanediol excretion in threatened abortion. The method used in this series was compared to another method and evaluated. Endogenous progesterone production was studied with radioactive progesterone. The 17-ketogenic steroids and 17-ketosteroids were estimated with and without progesterone loads in normal patients and those with chronic abortions.

Material

The accuracy of the diagnosis of threatened abortion, when made on cliric patients, is difficult to evaluate. Too many induced abortions will fall into the threatened-abortion group. For this reason a series of 357 private patients were followed during the years 1951 to 1959. Many of these patients were sterile or had suffered repeated spontaneous abortions. It was felt the incidence of induced abortion was reduced to a minimum. The 357 patients were divided in o two groups. Group I, numbering 274 prtients, were threatening to abort. The diagnosis was made by the history of bleeding and cramping in the first trimester plus the physical findings consistent with threatened above tion. Group II numbered 83 patients without , 196

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bieeding or cramping, who had suffered perious spontaneous abortions. The number of abortions varied from 1 to 9, but no emphasis was placed on this. Although some women in Group II had suffered 4 or more spontaneous abortions the purpose of this group was to evaluate low pregnanediol excretion in pregnant patients not actually threatening to abort. The pregnanediol levels and outcome of the pregnancies in each group were studied. The women were carefully instructed as to the method of collecting the 24 hour urine specimens. No treatment except modified bed rest was instituted before the pregnanediol levels were reported.

The patients in Groups I and II were divided according to high and low pregnanediol excretion. If the 24 hour output was less than 5 mg. the patient was placed in the low-excretion group and in the high group if over 5 mg.

Treatment was governed by the pregnanediol levels. The high-excretion group received no hormone therapy. The low-excretion group was given oral stilbestrol, 25 mg. daily, which was increased to 50 mg. daily at 4 months and 75 mg. at 6 months. The dosage was discontinued at 38 weeks. Some patients in the low-excretion group received in addition to stilbestrol, Delalutin,* 250 mg. to 500 mg. weekly, during the first trimester and, in some instances to 38 weeks. No attempt was made to evaluate the efficacy of the 2 drugs used. The results were simply the pregnancy outcome in the low pregnanediol excretion hormone-treated group, and the high pregnanediol non-hormonetreated group. Goldzieher and Benigno were mable to find reports of stilbestrol-treated patients who had abortions with low pregranediol levels determined by acceptable 1 ethods.17

This series of cases was not a consecutive series of threatened abortions. Some patients and cramping and bleeding and aborted in matter of a few hours, during which time 24 hour urine specimen was not collected.

In general, however, most patients had some warning at least 24 hours prior to abortion. Because of this no definite conclusions as to abortion rate and value of treatment can be made. The statistical outcome of the low and high pregnanediol excretions was determined.

Methods

The first chemical method of assaying progesterone was developed in 1937 by Venning.19 The method was gravimetric and involved an extraction of the urine specimen with n-butanol to remove the glucuronide of pregnanediol. The criticism of this technique was based on the presence of impurities which were precipitated with the glucuronide of pregnanediol. In addition, urinary pregnanediol glucuronide may be hydrolyzed to some extent by bacterial enzymes. Thus recovery of pregnanediol glucuronide varied from urine to urine. These results contributed greatly to the confusion existing as to the value of pregnanediol excretion studies in threatened abortions.

Astwood and Jones²⁰ employed acid hydrolysis in the presence of toluene to liberate free pregnanediol. Prolonged acid hydrolysis produces artifacts which may lead to misinterpretation with this method.

Talbot²¹ and also Sommerville²² modified the Astwood-Jones method. However, their attempts at purification did not significantly improve the accuracy of the procedure.

Recently Klopper and associates²³ reported a sensitive and accurate procedure for the determination of urinary pregnanediol. This method employed column chromatography on alumina before and after acetylation of urinary extracts. This method was used to evaluate the following procedure which was used in all the studies.

In 1952 Chaney²⁴ reported a method of utilizing acid hydrolysis and simultaneous extraction with isooctane. The extract was washed and chromatographed on a column using a mixture of Celite calcium carbonate. The material was eluted with 0.2 per cent of methanol in toluene and the eluate was taken to dryness. After the residue was

^{*17-}alpha-hydroxyprogesterone, E. R. Squibb & Sons, New York.

Table I. Comparison of pregnanediol values as done by the Klopper and Chaney procedures

Patient	Week of pregnancy	Klopper* (mg./day)	Chaney (mg./day)
T. D.	10	4.6	5.4
J. M.	5-6	7.1	8.9
E. M.	5	8.9	8.3
M.G.	5-6	4.2	2.8
D. S.	12	6.8	5.3
L. S.	6	4.2	3.4
J. T.	10 .	5.2	6.2
M. F.	9	1.7 less than	1.0
N.K.	7	12.0	4.1
I. M.	6-8	4.0	2.2
B. B.	10	10.0	8.7
C. R.	5	1.8	4.2
A. M.	6	8.6	13.0
E. C.	12	10.8	21.0
C. C.	12-14	5.8	9.0
M. T.	_	10.2	12.8
Average		6.3	7.3

*These values obtained after a single analysis.

washed with a small volume of cold isooctane, the remaining solution was taken to
dryness and developed with sulfuric acid.
The color was read at 3 wave lengths and
corrected for background absorption by the
method of Allen.²⁵ All the determinations
in this series were made by the Chaney
method at the A. L. Chaney Chemical Laboratory. The method was modified to include
permanganate oxidation prior to column
chromatography. This step eliminates pregnanetriol interference. The modified method
was compared to the method of Klopper
and associates on 16 specimens (Table I).

For the most part the methods were in agreement except the Chaney method which gave slightly higher results on the average. Enzymatic hydrolysis of steroid conjugates was found to be more suitable for metabolic studies than acid hydrolysis, but for purposes of evaluating threatened abortions such accuracy was not necessary.

Radioactive progesterone studies

As a preliminary study a small series of patients was evaluated as to group differences in endogenous progesterone production. Patients for this study were selected from the Los Angeles County General Hospital Olstetrical and Gynecological Service. The women were between 23 and 40 years of again and were admitted for diagnostic curettag. No palpable evidence of pelvic disease was present. Seven patients were studied—3 were normal without history of abortions and had a history of 3 or more abortions.

These patients were given radioactive progesterone intravenously and urine specimens collected over a 5 day period. This was repeated 1 month later after a "load" of 500 mg. of progesterone intramuscularly in aqueous suspension.

To calculate the endogenous production of progesterone the following assumptions were made: (1) The radioprogesterone administered intravenously as a single dose mixes very rapidly with the endogenous progesterone. (2) The rate of excretion of pregnanediol is a constant per cent of progesterone production. (3) The progesterone pool is small in comparison with the daily production of progesterone. (4) There is no other source of pregnanediol. With these assumptions the result is an equation of isotopic dilution.¹⁸

The excretion values of 17-ketosteroids and 17-ketogenic steroids were determined by standard methods²⁶⁻²⁸—on pooled specimens of 5 day collections.

Results

Analysis of the total group of 357 patients revealed 137 cases of low pregnanediol excretion and 220 of high pregnanediol excretion. The over-all abortion rate combining Groups I and II was 42.3 per cent in the low-excretion group and 14.5 per cent in the high-excretion group. The rate for the 274 threatened abortions treated depending upon the pregnanediol excretion was 28.8 per cent.

Group I. The Group I patients, these actually bleeding and cramping, revealed the most significant results (Table II). In this group 79 patients aborted, and of the e 79 patients, 57 were in the low-excretion group, constituting a 72.1 per cent incidence of abortion in this group. The results in this

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group of patients indicated that low preg-

nanediol levels in threatened abortion offer t poor prognosis and are in accord with previous reports. The 72.1 per cent abortion incidence in this group cannot be compared with previous rates of approximately 90 per cent because of the different methods of evaluating pregnanediol excretion and the differences in the groups of patients.

Group II. In Group II there were 83 patients, 15 of whom were low in pregnanediol excretion (Table III). These patients were started on the low excretion hormone regime when the reports were available. Only one of this group aborted. The number of cases is too small for analysis. However, a similar study on a larger series of patients suffering 4 or more spontaneous abortions would be of interest. Eleven patients aborted in the high-excretion group. Three of the abortions in this group were in the second trimester and occurred before cervical sutures were used for this problem.

Endogenous progesterone production. The production of endogenous progesterone was calculated as described previously. The results indicated that there might be differences in the production of progesterone in the two groups. In the normal group under basal conditions the total excretion of radioactivity in 5 days ranged from 30 to 69 per cent in the normal group and in the abortion group 30 to 56 per cent. The predominant portion of radioactivity was excreted in the first 24 hours. After the progesterone load, the total output of radioactivity in the abortion group was diminished approximately 20 per cent.

The endogenous production of progesterone differed in the two groups (Table IV). The patients in the normal group produced from 6.3 to 8.7 mg. of progesterone per day. In the abortion group, with the exception of patient, the daily production of progesterone was almost twice that of the normal patients. If metabolism were proceeding in a normal manner, a greater excretion of pregnanediol would be expected, but this was not the case. This finding suggests that the hormone is being metabolized via other path-

Table II. Group I*

*	
Total cases	274
Number of abortions	79
Incidence of abortions	28.8%
High pregnanediol excretion	
Number of abortions	22
Incidence of abortions	27.8%
Low pregnanediol excretion	
Number of abortions	57
Incidence of abortions	72.1%

*The abortion incidence divided into high and low pregnanediol excretion in the group of patients threatening to abort.

Table III. Group II*

Total cases	83
Number of abortions	11
Incidence of abortions	13.2%
High pregnanediol excretion Number of abortions	10
Low pregnanediol excretions Number of abortions	1

*The incidence of abortion divided into high and low pregnanediol excretion in the group of patients having a past history of abortions but not threatening to abort.

ways. The progesterone conversion to pregnanediol and pregnenolone revealed no striking differences between the two groups. In addition to these steroids, there were 11 other radioactive metabolites demonstrable by paper chromatography. There were radioactive products present in the polar fraction of normal patients which were not present in the abortion group. These compounds migrated more slowly than cortisone and are likely to be similar in structure to cortisone. The nature of these compounds was not determined. Future studies of these metabolites may prove fruitful.

17-Ketosteroids and 17-ketogenic steroids. Steroid determinations were done on 32 patients threatening to abort with bleeding and cramping. Five patients aborted and none of the 5 had abnormal 17-ketosteroid or 17-ketogenic steroid levels. Three patients aborted in the low-pregnanediol group of 13, and of the 19 normal-excretion patients 2 aborted. One patient did show low values for all steroids. The 17-ketosteroids were 3.5

Table IV. Endogenous production of progesterone

Patients	Progesterone (mg./day)
Normal group	
A. L.	8.7
A. W.	6.3
F. G.	8.5
Abortion group	
B. B.	11.7
J. B.	17.6
L. C.	19.6
J. D.	7.7

Table V. Urinary excretion of 17-ketosteroids and 17-ketogenic steroids

	17-Ketosteroids (mg./day)		17-Ketogenic steroids (mg./day)	
Patients	Basal	Load	Basal	Load
Normal group			,	
A. L.	12.0	15.9	19.0	5.9
A. W.	19.5	12.6	25.7	8.9
F. G.	9.7	5.7	10.2	7.4
Abortion group				
J. B.	7.9	9.4	6.9	8.8
L. C.	3.2	3.7	7.8	12.0
J. D.	6.6	11.1	8.7	8.0
В. В.	11.8		10.5	

(normal 6 to 15), the 17-ketogenics 4 (normal 4 to 15 mg.), and the pregnanediol, 2.4 mg. per 24 hours. This patient was later found to have a benign mole. Low pregnanediol levels in hydatidiform moles have been reported previously.²⁹

Steroid studies were also done on the pooled specimens of the 5 day collection in the group of patients receiving radioactive progesterone (Table V). The basal excretion of 17-ketosteroids and 17-ketogenic steroids appeared to be within the normal range, with the exception of 1 instance. The 17-ketosteroids and 17-ketogenic steroids in this patient were higher than normal. Under progesterone load the 17-ketosteroid excretion was depressed in 2 patients and was increased in the third patient. All 3 patients exhibited a marked decrease in the output

of 17-ketogenic steroids on progesterone

In the abortion group 2 women had excretion of 17-ketosteroids which were in the low-normal levels. A third patient excreted less than 5 mg. of 17-ketosteroids per day. The output of 17-ketogenic steroids for the group was within the normal range. Under progesterone load, the trend was toward an increase in both 17 ketosteroids and 17-ketogenic steroids.

Comment

The common factor of low pregnanediol excretion values in threatened abortion deserves close scrutiny and further investigation. In this small preliminary study of endogenous production of progesterone, the abortion group produced more progesterone than a group of patients having no history of previous abortions. This finding suggested possible abnormal progesterone metabolism in the abortion group.

By paper chromatography, radioactive metabolites were demonstrated in the polar fraction of normal patients which were not present in the abortion group. Further study of this group of metabolites could produce valuable information.

No definite pattern was seen in the 17-ketosteroids and 17-ketogenic steroids in the abortion group. After the progesterone load in the radioactive study, a difference was noted. The excretion levels increased after the progesterone load in the abortion groups and decreased in the normal groups. The significance of this was not apparent from this small series.

Conclusions

1. Low pregnanediol levels in patients threatening to abort offer a poor prognosis for the outcome of the pregnancy. In this series 72.1 per cent of the abortions fell in the low-excretion group.

2. High pregnanediol levels in threatened abortion offer a better prognosis. In the high pregnanediol group of threatened abortion patients, actively bleeding and cramping, the incidence of abortion was 27.8 per cent.

3. Low pregnanediol values in patients without active indication of abortion were of no prognostic value.

We wish to express our appreciation for the help and direction given us by Dr. B. J. Hanley and Dr. Stanley Krushinsky in the preparation of this paper.

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Discussion

Dr. Ivan Langley, Portland, Oregon. When me is presented with another fine paper on this confusing problem, it makes one as defensive as the physician who is plagued by detail men and who, confronted with a startling new drug, resists in this sequence.

- 1. Detail man: This new drug cured 98 per ent of 4,000 cases treated. Physician: The drug as not been tried enough and is not important.
- 2. Some time later: We have now treated 45,000 cases with good results. *Physician*: I am certain 44,000 cases do not in themselves prove the value of the drug.
- 3. Some time later: We have now treated 44,000 cases with excellent results. Physician:

This certainly proves the drug, but the expense makes its use impractical.

4. Some time later: We have now treated 4.4 million cases with excellent results, and the cost has been cut by 65 per cent. Physician: I realize this drug is proved, safe, practical, but do not bother with a drug that is not new.

I am not willing to admit that this pregnanediol excretion determination, significant though it might seem, is either practical, proved, or new. On any of these points I am willing to concede, in the future, if the following points are made clear.

1. That the total abortion rate is significantly changed by any type of therapy.

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2. That low pregnanediol excretion per se is significant in any pregnant patient, not just those threatening to abort.

That the metabolic fate of exogenous progesterone mimics exactly that of endogenous progesterone, and that its effect upon the develop-

ing pregnancy is also the same.

4. That the issue of cause and effect be clarified in low pregnanediol excretion in relation to abortion, i.e., does the low pregnanediol level reflect the impending tendency to abort, whatever the cause, or does the potential cause of the abortion in some unexplained manner reduce the pregnanediol excretion?

In short, while I laud Dr. Langmade's efforts to shed some light on this baffling problem, I think this and many other excellent papers on the same subject share a major deficiency. I have yet to believe that any form of therapy, from bed rest to complicated steroids, Hesper-C to vitamin E, has a sufficient effect upon changing the abortion rate in a discernible degree.

Until such new methods are developed which will enable us to determine the status of the embryo, growth, and viability of its structures of support at any time in pregnancy, indirect investigations such as this may well help to show the way to more practical prognostic measures.

I would like to ask Dr. Langmade if any of the 19-nortestosterone drugs, in addition to stilbestrol and progesterone, were used therapeutically in the cases of low pregnanediol excretion.

Dr. William Dignam, Los Angeles, California. Determination of a critical level of pregnanediol excretion for the individual patient is of dubious value. In general or on the average, one probably can demonstrate a difference in the fate of these pregnancies if the pregnanediol excretion is above 5 mg. or below that amount.

In a group of patients like this, who are already bleeding, there is a possibility that the pregnanediol is low because the placenta has partly separated or partly degenerated. It is also true that an individual patient with a low pregnanediol level may go successfully through pregnancy, and a patient with a high level may abort. Perhaps the patient with the high pregnanediol level has some cause for the abortion other than a hormonal one, such as a defective fetus.

Why some persons with low pregnanediol levels go uneventfully through their pregnancies may be explained by the possibility that urinary pregnanediol bears little relation to the level of the progesterone in the blood in the uterus. In order to try to clarify this point, we and others are trying to obtain blood from the uterus or from the ovaries and compare it with peripheral blood to see if the two are constantly related.

Regarding Dr. Langmade's efforts to determine endogenous progesterone production and what relationship this may bear to subsequent pregnancies, we and others have measured progesterone in the corpus luteum and in the blood from the corpus luteum, and I think that the general level of progesterone production for a full menstrual cycle is about 200 mg.

DR. LANGMADE (Closing): To answer Dr. Langley's question concerning drugs used for treatment, we should emphasize that we did not attempt to evaluate any of the drugs used. This was a simple study of the outcome of patients threatening to abort who had low pregnanediol values.

Dr. Dignam has done a great deal of work with pregnanediol excretion and I value his comments very highly. It is true that for the individual patient a high or low level did not give us a specific answer. Clinically, however, we knew a low-excretion patient had a greater chance of aborting or having a missed abortion, and for this reason, we felt the levels were of clinical value. Most useful clinical tests today are not 100 per cent accurate.

Unusual lesions of the reproductive tract in infants and children

JAMES V. MCNULTY, M.D. NEWLIN HASTINGS, M.D. Los Angeles, California

THE Pacific Coast Obstetrical and Gynecological Society has an enduring familiarity with problems in pediatric gynecology through the excellent work of Schauffler¹ in the North and Henriksen²⁹ in the South. So, it is with a feeling of trepidation and temerity that we report on our experiences at Childrens Hospital in Los Angeles.

Material and sources

A 10 year period from January, 1950, to January, 1960, was selected. The study encompasses 154 cases of unusual lesions in the reproductive tract. Functional tumors and other neoplasms of the ovary are deleted, since they have previously been reported from Childrens Hospital.² Patients' ages range from a few hours to 17 years. The patients are referred by pediatricians or general practitioners from various areas in Southern California. Upon discharge from the hospital they are returned to the referring physicians. Long-term follow-up is not always possible.

All cases fall into the etiological categories shown in Table I. Obviously, there is considerable reduplication of case incidences. These will be enumerated, but only those of unusual interest or those from which something has be learned will be detailed.

I. Trauma. There are 15 cases involving trauma¹ to the genitals. The majority of these were "straddle-type" injuries, while there is one case of second and third degree burns of the vulva. The ages range from 16 months to 11 years. The external genitals seem to be well protected from serious traumatic involvement.

Case history. The patient was a 4½-year-old girl who, while riding a tricycle, overturned and fell astride the upright bar of the steering mechanism. The mother brought the child to the admitting room because of brisk hemorrhage from the external genitals. Careful examination revealed the fourchette and perineal body to be lacerated. Catheterization showed clear urine. Endoscopic examination of vagina revealed no free blood or foreign body. Rectal examination showed no perforation. Under halothane and cyclopropane anesthesia, suture of the laceration was carried out for hemostasis. Tetanus toxoid was given as a matter of routine.

II. Foreign body. There were 18 cases of foreign bodies. The age groups varied between 4 and 10 years. The foreign material recovered included bobby pin, paper clips, plastic toys, metallic bells, crayons, and buttons. General anesthesia was necessary in the cases where the object had had time to become embedded.

Case history. The patient was a 4-year-old girl with a history of vaginal spotting cyclically from birth to age 2. During the preceding year the child had had a recurrent, foul-smelling, sero-purulent, and sometimes bloody vaginal discharge. Vaginal smear was done by private

From the Childrens Hospital.

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Table I. Classification of lesions of reproductive tract

15
18
23
16
72
10
154

Table II. Inflammations of reproductive tract

Labial adhesions	12	
Diabetic vulvovaginitis	2	
Moniliasis	3	
Cellulitis and necrosis of vulva	2	
Beta streptococcus vaginitis	1	
Vulvovaginitis, unknown	3	

Table III. Neoplasms of reproductive tract

Sarcoma botryoides	4
Hydrocele of round ligament	2
Hymenal cysts	2
Condyloma accuminata	2
Verruca accuminata	1
Lipoma of vulva	1
Ectopic clitoris	1
Hemangioma of vulva	3
Total	16

Table IV. Congenital abnormalities of reproductive tract

P	Prolapse of uterus	2	
I	ncarcerated uterus, tubes,		
	ovaries in inguinal hernia	7	
F	usion of labia	. 8	
I	mperforate hymen	6	
N	Mucocolpos	1	
F	Hypertrophy of clitoris		
	(without adrenal disease)	5	
F	Rectovaginal fistula (associ-		
	ated with imperforate anus) 7	
(Congenital absence of		
	uterus and vagina	1	
I	Duplicate vagina and uterus		
	didelphys (associated with		
	anomalies of other systems)	6	
F	seudohermaphroditism		
	(female with ovaries)	25	
F	seudohermaphroditism		
	(male with testes)	3	
7	True hermaphroditism	1	
7	l'otal l	72	

doctor 3 months prior to admission. It was reported as showing gram-negative cocci and the diagnosis of Neisserian infection was made. The patient was treated with penicillin and a remission of symptoms occurred. Vaginal discharge recurred 3 weeks prior to admission, and a course of streptomycin and sulfonamides was given. However, the vaginal discharge continued and the patient was referred to Childrens Hospital.

Scout x-ray of the pelvis in the Emergency Clinic was reported as negative for foreign body.

Examination under general anesthesia was made and an embedded plastic toy was found high in the posterior fornix. This was removed.

III. Inflammation. Table II shows the various lesions seen under the category of "Inflammation." Patients range from 7 to 11 years in age.

Case history. The patient was a 7-year-old girl with a history of a recurrent, pruritic rash around the external genitals since the age of 2. The mother is divorced and claimed that the rash is always worse after the father takes the child for the court-allowed visit. The mother insisted that the father molests and handles the child. She has gone to considerable expense in pushing the courts for full custody. She has taken the child to numerous doctors in an effort to establish that the father actually causes the rash on the child by acts of perversion.

Physical examination showed several small, reddened papules on the mons pubis. The glands and urethra appeared normal. The fourchette was slightly reddened. Vaginoscopic examination failed to disclose a foreign body. Smear and culture were negative and no pinworms were present. Intravenous pyelography and cystogram findings were both normal.

Dermatological consultation was obtained. The diagnosis of neurodermatitis was made. The rash improved with tripelennamine cream.

The mother is currently being seen for psychiatric evaluation and help.

IV. Neoplasms. Table III outlines the neoplasms that were seen during this 10 year period. Only 2 cases of sarcoma botryoid's can be substantiated as arising primarily in the vagina. Hydrocele of round ligament, hymenal cysts, and ectopic clitoris perhaps should more correctly be considered under congenital abnormalities.

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Table V. Functional disorders of unknown eviology

Dysfunctional bleeding	3
Amenorrhea	1
Precocious puberty	6
Total	10

Case history. The patient was a 2½-year-old girl with the complaint of vaginal bleeding and dysuria for 1 month. Development to this time had been completely normal. Pregnancy and delivery had been uncomplicated. The family history was essentially normal and siblings are normal.

Findings on physical examination were essentially normal except for the genitals. There were bilateral inguinal lymph nodes. With the combined rectal and suprapubic pressure, gelatinous tissue was expressed from the vaginal orifice. The patient was markedly anemic, with a hemoglobin level of 7 Gm.

Chest x-ray examination showed some indistinct nodes in the left chest. Inguinal biopsies and tissue expressed from the vagina were reported by the pathologist to indicate rhabdomyosarcoma with metastases. A total hysterectomy, culpectomy, and inguinal node dissection were done.

On follow-up at 6 months, a fluid wave was noted in the abdomen. Paracentesis was positive for sarcoma cells. X-ray examination of the abdomen showed evidence of widespread abdominal metastases. Three courses of nitrogen mustard, totaling 1.5 mg., were given without response. The patient's condition deteriorated rapidly and she died 10 days after admission. Postmortem examination was not done.

V. Congenital abnormalities. Congenital abnormalities are shown in Table IV. The ages range from 1 day to 12 years.

Case history. The patient, a 9-year-old white child, was raised as a boy. He had been circum-esed shortly after birth and the diagnosis of expospadias and cryptorchidism was made. The child had received extensive hormonal therapy (anterior pituitary hormone and testosterone) for cryptorchidism. Because of his unusual liking for girls and feminine things, together with his dislike for sports, such as baseball, he was referred to Children's Hospital for sex determination.

The first buccal smear was negative for nuclear sex pattern. The second smear was positive (revealed female sex).

Findings on physical examination were not remarkable except for the external genitals. A phallus with an indistinct ventral groove ending in a urethral meatus was noted. The large labialike structure contained no testicles. No vaginal orifice could be seen. Cystoscopy was negative. The level of 17-ketosteroids was normal. Laparotomy revealed normal uterus, tubes, and ovaries.

Since the child had strong female identification, it was decided to raise this child as a girl. The parents and numerous consultants concurred with this decision. A clitorectomy and separation of fused labial folds was carried

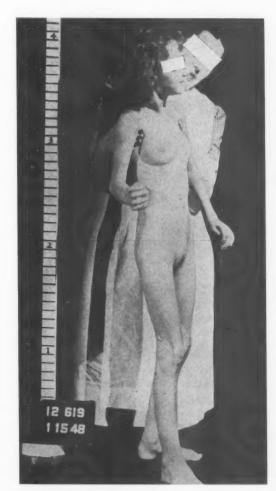


Fig. 1. Precocious puberty associated with central nervous system disease.



Fig. 2. So-called ectopic clitoris (probable supernumerary nipple).



Fig. 3. Hypertrophy of clitoris associated with adrenogenital syndrome.

out. A letter was sent to the Bureau of Vital Statistics in the state where the child was born, requesting sealing of the birth certificate issued for Michael, and an entirely new one was issued for Michelle. At follow-up examination one year later the patient is well adjusted and was oriented as a female.

VI. Functional disorders. Table V summarizes the functional disorders of unknown etiology seen in infants and children. This category was created and more or less re flects our ignorance in regard to these cases

Case history. The patient was an 8-year-old white girl who had a 2-year period of normal growth following a normal birth and neonata period. There are no unusual prenatal disease reported in the mother.

At the age of 2, the patient began having petit mal, and then generalized convulsions. A age 5, she had a sudden episode of left hemiplegia and loss of speech. Mental deterioration and retardation supervened rapidly.

For the past 6 months the breasts were noted to be rapidly enlarging, associated with the development of pubic hair. Pneumoencephalogram revealed slight hydrocephalus and cerebral degeneration. Electroencephalogram showed typical petit mal patterns. All of the studies were negative, including the level of 17-ketosteroids. X-ray findings of long bones was normal for a child of this age.

Physical examination showed a thin, poorly developed, and poorly nourished girl (Fig. 1). There was no facial expression. She was dull and not orientated. Pertinent findings included left hemiplegia. The breasts were moderately hypertrophied. Axillary hair was thin, and pubic hair moderately profuse. The patient was followed for 3 years. No menstruation occurred. She was committed to Sonoma State Hospital.

Comment

I. Trauma.¹ Injuries to the genitals are always a frightening experience to the parents. Because of the excellent blood supply to this area, lacerations usually result in brisk and alarming hemorrhage. Due to the age group involved, lack of cooperation necessitates general anesthesia for repair of affected parts; 5-0 chromic catgut is used as suture material. Perforations of the bladder and rectum must be ruled out and a diligent search made for foreign bodies. Tetanus prophylaxis is mandatory. Close observation for 24 hours is desirable.

II. Foreign bodies.¹ Gram-negative cocci are frequently seen in smears of vaginal discharge. The diagnosis of gonorrhea should not be made without culture of the organism, as was done in the case presented. Furthermore, x-ray examination should

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rever be relied on to rule out foreign bodies since most plastics are nonradiopaque. A glass stirring rod used to explore and sound the vagina is of great value. An old-fashioned Kelly endoscope to visualize the vaginal contents and cervix is indispensable. It is well to remember that there may be more than one foreign body present.

III. Inflammation.^{1, 3} We feel that many cases of vulvovaginitis exist in the minds of the parents. Somehow or other a runny nose escapes attention, but a runny vagina conjures in the minds of the parents a horrible disease. Some inflammations are iatrogenic in origin—for instance, secondary to treatment of systemic disease with the mycin group of drugs. We have found no cases of pinworm infestation. Poor toilet hygiene and nylon or rayon panties and pajamas induce many cases of vulvitis. Proved cases of gonorrheal vulvovaginitis have not been encountered.

IV. Neoplasm.^{4, 5, 28} Primary sarcoma of the vagina is extremely rare. Review of the literature shows only about 40 well-authenticated cases. The patients affected are between 2 and 3 years, but it is difficult to assay the duration from first appearance of the tumor until clinical diagnosis has been made. The case histories do not vary markedly from those cited. In spite of operation and radioactive therapy, the end results are most disappointing. Schuchardt and McFarland¹⁶ reported 2 cures. Ectopic clitoris (probably supranumerary nipple) is shown in Fig. 2.

V. Congenital abnormality. There were an unusual number of pseudohermaphrodites, 8 of females with ovaries associated with the adrenogenital syndrome, as seen in Fig. 3. About half of these patients had sollings with the same abnormality. Six patients were circumcised by the obstetrician in charge (Fig. 4). It is most urgent that sex determination be made as soon after both as possible.

Smears⁹⁻¹⁵ are of great help in establishing sex accurately. The method is quite simple. Great advances are being reported in the foreign literature with tissue cultures



Fig. 4. Pseudohermaphrodite, female with ovaries, circumcised at birth.

and the identification of sex chromosomes. Laparotomy with biopsy of the gonads is well tolerated by the newborn. The obstetrician should have no reluctance to perform this procedure. The infant is still his responsibility until he surrenders it to the pediatrician. It is our opinion that it is usually most unwise to make any changes in sex after 2 years—particularly if the child has been reared as a male and has strong inclinations in that direction.

Prolapse of the uterus¹⁶ is unusual, but it is always associated with spina bifida. This would indicate faulty innervation to the urogenital diaphragm. One of the cases of clitoral hypertrophy without adrenal dysfunction was felt to be due to the maternal

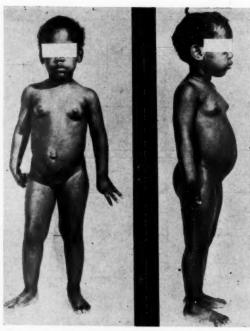


Fig. 5. Constitutional precocious puberty.

ingestion of 17-ethinyl testosterone.¹⁷ The mother had had habitual abortions, and was placed on the above medication from the fourth week of pregnancy until the thirty-seventh week.

Labial adhesions^{18, 19, 20} are felt to arise as a result of mucolytic enzymes secreted by the vagina, or possibly from inflammatory causes. Treatment is not indicated unless there is interference with the urinary stream. Spontaneous cure may be anticipated around 8 years of age.

Imperforate hymen^{21, 22} is frequently a silent disease. It is surprising to note that difficulty in voiding is an outstanding symptom and so often is the only subjective complaint.

Hernia²³ of the pelvic viscera is usually made at the operating table and every effort must be made to preserve intact the organs of reproduction.

Congenital absence of the vagina^{24, 25} is a tragedy indeed. We do not agree that vaginoplasty should be postponed until the patient becomes engaged to be married. We know of one girl who experienced 3 broken

engagements as a result of telling her fiance what their problems would be. Early vaginoplasty is recommended to establish a trace which can then be enlarged when the times is more propitious.

VI. Idiopathic. Dysfunctional bleeding was seen in 3 cases. One is dismayed at the reluctance of the physician to resort to curettage in the prepubertal group. Patients are permitted to bleed until the hemoglobin level is low, while the doctor temporizes with "hormone, styptic, and hematinic shots." One patient, aged 12, had a hemoglobin level of 7 Gm. She had been under various forms of treatment for one year. She presented a history of menometrorrhagia. Curettement showed a large endometrial polyp and cystic hyperplasia of the endometrium.

Precocious puberty^{26, 27} developed in 6 cases during the past 10 years. All but one patient had an antecedent history of central nervous system disease, such as encephalitis, meningitis, or epilepsy. The remaining case (Fig. 5) it is felt, represents a typical case of constitutional precocious puberty, as described by Novak.³⁰ No effective treatment is known for this condition.

Summary

A 10 year review of interesting lesions of the reproductive system is reported from Childrens Hospital in Los Angeles. One hundred fifty-four cases are outlined, and illustrative cases are delineated. The lesions elucidated include trauma, foreign body, inflammation, neoplasm, congenital abnormality, and idiopathic disease.

Conclusions

1. This paper has attempted to extract the clinical material seen at Childrens Hopital relating to the reproductive organs of infants and children. It should be undestood that many cases are lost because they were simply seen in the outpatient department, and the patient was not admitted to the hospital for study.

2. These cases represent a fair crossection of pathology which a gynecologist

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may expect to encounter in the reproductive tract at a hospital for infants and children.

3. Pediatric gynecology is a most interest-

ing, challenging, and rewarding field to the obstetrician-gynecologist. Much remains to be learned.

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Discussion

Dr. Edmund W. Overstreet, San Francisco, California. Among the 6 categories into which Dr. McNulty's cases are classified, almost one half of his patients fall into the group with congenital abnormalities. This points up our increasing recognition of such anomalies, and the importance of their early diagnosis. Some are very easily overlooked. Many are totally asymptomatic in early years. As a result, misidentification of sex of the newborn is much more frequent than it should be. Here again Dr. McNulty's figures are significant, for one third of his patients with congenital anomaly were pseudohermaphrotites (28 cases) and the ratio of male to female reseudohermaphrodites was 1:8. The female type then is quite common; and the diagnosis is often missed at birth, the child being mistaken for a boy with hypospadias and undescended testes. In my opinion all such infants should have immedi-

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ate Barr counts of chromosomes at birth sufficient to establish the genetic sex unequivocally.

Dr. McNulty has quite properly emphasized the importance of making such a diagnosis early in life in order to avoid the psychological problems produced by the reversal of the somatic, sex-rearing pattern at too late an age. But I am dubious about the vigor of his advice against accomplishing such reversal after the age of 2 -especially for female pseudohermaphrodites. Maintaining them as boys simply because the diagnosis was made too late means major operation and total sterility. Conversion to a more normal female means a good chance for better sex function and even childbearing. Some authoritative psychiatrists maintain that the psychological hazards are not as gloomy as they have been painted.

I am slightly unhappy also over Dr. McNulty's

dismay at the reluctance of most physicians to resort to curettage in the pubertal group of patients with abnormal bleeding. Here again, as in the female pseudohermaphrodites, the balance to be struck is between the psychological trauma of hospitalization, anesthesia, curettage, and the degree of real need for the procedure. Almost all pubertal bleeders-what Dr. Page has called "the bobby-sox bleeder"-have repeated anovulatory cycles and cystic endometrial hyperplasia. With our present efficient methods of hormonal medical curettage there is no need for such patients "to bleed until the hemoglobin level is low." As has been repeatedly said, "tincture of time" is the best definitive therapy for this problem. Naturally, when truly worrisome, debilitating bleeding persists in the face of skillful conservative management, curettage becomes imperative. But this is very rare indeed.

It is so rare that I am startled and intrigued by Dr. McNulty's report of a case of a large endometrial polyp recovered by curettage from a 12-year-old girl. In Newgard and Morton's paper reporting 82 cases of endometrial polyposis their youngest patient was 24 years old. I have recently reviewed 400 consecutive cases of endometrial polyposis from our hospital, and the youngest patient was 15 years old. I am delighted to add Dr. McNulty's even younger case to our knowledge of this condition.

Dr. G. C. Schauffler, Portland, Oregon (read by Dr. C. F. Fluhmann). With apologies to Dr. McNulty, here are some conditions which are of interest chiefly because they are easily subject to misdiagnosis, and thus may lead to ill-advised treatment.

The first case was that of a little girl 5 years old sent to me with the diagnosis of Gartner cyst of the lower vagina. Under light thiopental, the situation was investigated with a protective finger in the rectum and a sound in the urethra and bladder. The cyst was then found to be a protruding saccular hymen behind which there was a collection of several cubic centimeters of clear mucoid secretion. The protruding cyst was circumcised. The vagina was then examined and found to be normal together with the rest of the immature genitals.

The second patient, a girl aged 6, was sent to me with a diagnosis of necrotic prolapse of the hymen; and this, indeed, at first examination it appeared to be. The entire vestibule was crowded by the unpleasant looking and unpleasant smelling tumor. Under light thiopental, with the usual rectal and urethral protection, we easily discerned a prolapsed urethra with subsequent swelling and necrosis. The temptation to cicumcise this prolapse which is more or less routine treatment, was not indulged. Hot packs and antibiotics caused a rapid regression of infection and swelling, and the condition cured itself.

It is interesting that this child at no time complained of dysuria or other pain or discomfort. The customary treatment of such accidents is generally circumcision of the prolapsed portion of the urethra with approximation of skin to mucosa. The operation and its sequellae are amazingly simple and easy. The condition is actually not too uncommon. It is submitted here because it confuses the diagnosis, as we have indicated. From its appearance and general characteristics, this might have been mistaken for a cancerous growth.

The third case raises an interesting question for diagnosis. The patient was a 4-year-old girl with no symptoms except local tenderness and mild discomfort. The condition proved to be a simple annular prolapse of the lower fourth of the immature vagina. Here again surgical treatment which might have been effective was not required. Hot packs, knee-chest position, and gentle pressure reduced this hernia which remained in place. We have seen the child subsequently. The defect here involves a type of hereditary lack of vaginal support, which seems to underly the sort of thing we see when cystocele and rectocele and/or vaginal prolapse or enterocele occur in nulliparous women. There is a fairly well-known congenital insufficiency of supports. This child might be expected to have trouble in later life and especially following childbearing.

The fourth case is that of a 6-year-old child who had a thickened whitish perivestibular area, grossly indistinguishable from leukoplakia or kraurosis as defined in elderly women. By Huffman it is now called lichen vel atrophicus, which is a dandy Latin name. The punch biopsies from this area were submitted to several first-rate pathologists simply as vulvar biopsy. The tissue diagnosis was mild kraurosis or leukoplakia desiccans. Leaving aside arguments on the refinments of such diagnoses, we have seen a good many cases of this sort. They are much less symptomatic than in elderly women, but see a to us to represent the same anestrogenic status.

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The vagina, for example, in these girls presents a situation indistinguishable from senile vaginitis. Although there seems to be an obvious connection between this condition in children and the classical lack of estrogen at this age (6), treatment with estrogen does not clearly corroborate such an association. It should be used, however. Radical measures are, in our experience, never called for, and cure is spontaneous with upsurging estrogen of adolescence.

DR. HAROLD M. LYONS, San Francisco, California. The largest number of patients in this series were those having congenital anomalies, and the largest number of congenital anomalies were those of pseudohermaphroditism. Dr. Mc-Nulty mentioned the fact that there was a tendency for these congenital anomalies to be repeated in the same families. Dr. Overstreet in his discussion suggested that some of these congenital anomalies can be surgically corrected to the extent that childbearing may result. I feel strongly that such thinking is more motivated by empathy and sympathy than by logic and reason. Congenital anomalies of this nature are lethal mutants. Any attempt to alter these mutations to the extent that reproduction is the end result is to me odious from a eugenic standpoint. The constant surgical correction and re-introduction of congenital defects into the general population can be as lethal and less acceptable than the mutations unintentionally produced by irradiation from medical sources or secondary to atomic explosions.

Dr. Russell R. De Alvarez, Seattle, Washington. The essayist referred to the typical case of congenital adrenal hyperplasia with a normal

17-ketosteroid level. This has not, in our experience, been the usual situation. The 17-ketosteroid level is usually elevated, even though in young children there are different standards of normal for children. The Joneses, in Baltimore, have described a group of cases of congenital adrenal hyperplasia with normal 17-ketosteroid levels. However, in that same group of patients they had not measured pregnanetriol, which is usually excreted by these patients. It represents a metabolite of 17-OH progesterone and, if this is present, the diagnosis of congenital adrenal hyperplasia may be entertained.

Dr. McNulty (Closing). That Dr. Overstreet did not criticize us regarding this mutilating procedure of clitorectomy surprised me. I myself have never performed a clitorectomy on these cases. It is usually done on the advice of the psychiatrists.

I would like to emphasize the reluctance on the part of so many about performing curettage in the pubertal age group. The case of the endometrial polyp could never have been cured by medical methods, yet the girl was permitted to bleed until she had a low level of hemoglobin. We tried to emphasize that a dilatation and curettage is oftentimes necessary to make a diagnosis and produce a cure for unusual bleeding.

At Childrens Hospital, we often see cases of urethral prolapse and so often it is mistaken for prolapse of the hymen. I do want to stress that one should avoid the use of estrogenic creams and ointments for treatment of various forms of vaginitis and vulvitis. Often permanent vulvar and nipple pigmentation will result. This frequently is a traumatic psychological experience for the child.

Enterocele

A study of 265 cases

GERALD E. KINZEL, M.D. Portland, Oregon

The first formal description of enterocele is attributed by Bueerman¹ to Garengeot in 1736. As late as 1932 enterocele was considered a rare clinical entity, and Bueerman¹ collected only 86 recorded cases.

Although the literature on enterocele has now become more voluminous, there are few large series of these cases recorded. Those of Weed and Tyrone,² Phaneuf,³ Austin and Damstra,⁴ and Charles Reed⁵ are among the most comprehensive.

By definition, an enterocele is any herniation of the small intestine into the vagina. An enterocele, in contrast to a rectocele and a cystocele, is a true hernia and not a sliding hernia. An enterocele, being a true hernia, has a sac, neck, and contents. The neck of this sac is between the uterosacral ligaments in front of the sacrum and behind the cervix, if it is present. This hernia slips through the endopelvic fascia and down the posterior fornix in front of the sacrum and behind the cervix, if it is present, and in its most extreme form may emerge at the perineal body. A rare type, the anterior vaginal hernia, may dissect between bladder and uterus. Where a redundant cul-de-sac ends and an enterocele begins is only of academic interest in the correction of this condition.

There are many synonyms for enterocele, such as posterior vaginal hernia, primary and secondary enterocele, cul-de-sac hernia,

Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Yosemite National Park, California, Sept. 28-Oct. 1, 1960. pouch of Douglas hernia, and rectovaginal hernia. Popular usage has made the word "enterocele" best known. The use of these other terms, while descriptive, should probably be discontinued to avoid future confusion.

Reed,⁵ the great English gynecologist, classified enteroceles into two types: the pulsion type caused by intra-abdominal pressure from above and the traction type associated with prolapse or descent of the uterus and vagina from below. In this paper all peritoneal sacs associated with the uterus present or absent and with or without uterine prolapse were included. Only the complete prolapse of the vaginal vault was omitted in this study, although in the broad sense it could be termed an enterocele. It was felt that this defect deserved its own niche in pelvic terminology.

Etiology

Reed,⁵ in an excellent review of the etiology of enterocele, gives credit to Cuneo and Veau for their early studies on the cul-de-sac. He praises Uhlenhuth and associates⁷ for their comprehensive study of the embryology and anatomy of the pouch of Douglas. The essence of the thesis of Uhlenhuth and his co-workers⁷ is as follows:

In the fetus the cul-de-sac of Douglas often extends to the perineal body and is depth gradually decreases in a caudad direction until term, when it reaches the level of the second or third sacral vertebrae. This congenital pouch is usually closed in fetal life by dorsal ventral fusion of the perito-

neum, thus forming the rectogenital septum. The degree of fusion varies from none to complete, thus giving various depths to the cal-de-sac. The strength of the fascial investments about the cul-de-sac varies as it does is hernias elsewhere in the body. Reed, quoting the researches of Cuneo and Veau, Kirk, and Uhlenhuth and associates, felt that the congenital elongated sac is often present from birth and the analogy to the preformed sac of hernias generally becomes obvious in this condition. He goes on to stress that generalized enteroptosis adiposity, allowing the organs to drop down deep in the pelvis, may cause distressing symptoms when the patient is standing.

Clinical material

Two hundred sixty-five consecutive cases were surveyed from the charts of two general hospitals in Portland, Oregon; 180 were reviewed at the Emanuel Hospital during an 8 year period (1950 to 1958, inclusive); 85 were reviewed at the Good Samaritan Hospital during the same period of time. In both of these hospitals this type of operation was performed by gynecologists and only rarely by general surgeons.

There are probably many more unrecorded recurrent enteroceles in this series, as follow-up beyond the immediate hospital stay or readmission was impossible.

In discussing vaginal hysterectomy with relation to enterocele correction, it should be pointed out, as it was by Benson,⁶ that almost 90 per cent of 1,000 vaginal hysterectomies reviewed at the Emanuel Hospital also included associated vaginal plastic operations. All the cases described in this series had additional anterior and/or posterior colporrhaphies.

Age. The youngest patient in the present series was 26 years old and the oldest was 7%. Table I shows that the greatest number of enteroceles occur from the age of 50 to 70. This is in agreement with reports of other authors. 2, 4

Parity. The parity of these patients is shown in Table II. It is suggested that parity probably plays a role in enterocele for-

mation. The connection as pointed out by Austin⁴ may be more coincidental than etiological. He states that "one difficult traumatic delivery may do more to procure enterocele than 9 normal, relatively easy deliveries." Only 15 or 6 per cent of the 250 patients studied with parity known had never borne children. Of these 15 nulliparous women, only 4 had had no previous gynecologic operations. Two of these 4 had had a prolapse of the uterus. Thus, only 2 patients of the 250 studied had a true congenital enterocele.

Of the remaining 11 nulligravidas, 8 had had abdominal hysterectomy, and 3 had had abdominal gynecologic operations. In these nulligravid patients with enteroceles, the symptoms were chiefly urinary rather than rectal. Reed reported 16 nulligravidas in his series of 167 cases.

Previous operations. As is shown in Table III, previous operations preceded enterocele formation in 142 of the 265 cases studied. In the 142 cases 57 vaginal hysterectomies preceded the enterocele formation, 52 abdominal hysterectomies, 28 various forms of vaginal plastic operations, and 22 abdominal suspensions. The balance of miscellaneous

Table I. Ages of patients with enterocele

	Emanuel Hospital	Good Samaritan	Total
20 to 29	2	3	5
30 to 39	5	16	21
40 to 49	36	19	55
50 to 59	58	18	76
60 to 69	56	20	76
70 to 79	24	8	32
Total	181	84	265

Table II. Parity of patients with enterocele

Parity	Emanuel Hospital	Good Samaritan	Total
Not known	9	6	15
0	13	2	15
1	24	11	35
2	32	30	62
3	28	21	49
4	17	10	27
5 or more	30	5	35
Total	153	85	265

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Table III. Types of previous operations in 142 patients

	Eman- uel	Good Sa- mari- tan	Total
Vaginal operations			
Anterior colporrhaphy Cystocele and rectocele	1	0	1
repair	19	3	22
Excision of cervical stump	1	0	1
Interposition operation	1	0	1
Manchester operation	4	1	5
Perineal repairs	0	2	2
Recurrent enterocele			
repair	3	0	3
Spaulding-Richardson	0	1	1
Vaginal hysterectomy	43	14	57
Abdominal operations			
Supravaginal hysterectomy	20	7	27
Suspension operation Total abdominal hyster-	14	8	22
ectomy	20	5	25
Miscellaneous operations			
Cancer of rectum (ab-	0	0	0
dominal perineal)	2	0	2
Cesarean section	2	0	2
Colonopexy	1	0	1
Inguinal hernia	1	0	1
Myomectomy	3	0	3
Salpingo-oophorectomy	1	1	2
Vulvectomy	1	0	1
Total	137	42	179*

*Some patients had more than one operation to account for the total of 179.

operations was not significant. There was a surprisingly low rate of recurrent enteroceles —only 3.

Although the high number of vaginal hysterectomies preceding enterocele formation did not surprise us, the almost as high number of abdominal hysterectomies did. Perhaps many of these abdominal hysterectomies should have been vaginal operations so that repair of an existing enterocele and rectocele could have been accomplished. If this is not done, perhaps a more liberal application of a prophylactic Moschcowitz operation should be used. Reed, especially, feels that anterior abdominal fixation is responsible for direct thrust into the cul-desac with pulsion type of enterocele.

It should again be emphasized that an abdominal or vaginal hysterectomy alone

will not cure or prevent enteroceles. In Reed's series from England vaginal hystenectomies seldom were done. Plastic operations for uterovaginal prolapse lead his list followed by ventrofixation procedures. He seldom saw an enterocele preceded by an abdominal hysterectomy.

No previous operation. In this series 46.1 per cent (123 of 265 patients) had never had an operation. Enteroceles were found in 29 per cent of the patients with no previous operation by Weed,² 40.5 per cent by Austin,⁴ and 53.3 per cent by Reed.⁵ As pointed out in Table IV, enterocele was most often found during vaginal hysterectomies and vaginal plastic operations and rarely recorded during abdominal operations.

Enterocele was probably present more frequently in abdominal procedures than this study indicates. The cul-de-sac should be explored visually and digitally. Weak as the uterosacral ligaments often appear, their approximation aids materially in preventing future herniation of the small bowel between them.

Symptoms

The classic symptoms of an enterocele are said to be rectal, such as pressure in the rectum, bulging mass in the vagina, feeling of fullness, inability to defecate, or a feeling of incomplete emptying of the bowels (Table V). The rectal symptoms were mentioned in only 51 cases and a bulging mass in 97 cases. Urinary symptoms were noted 97 times and the enterocele was often found incidentally. Prolapse symptoms were noted 81 times. Spotting and discharge were infrequent symptoms. This is in direct contrast to Weed's statement of finding predominantly rectal symptoms. Thus, enterocele must be thought of and specifically looked for. This is particularly true at the time of vaginal as well as abdominal operations. Weed and Tyrone and Reed alo emphasize this.

There was no consistency in the duration of symptoms, but the great majority of patients had symptoms of less than one

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year's duration. There was also no consistency in the time elapsed between previous operation and recurrence of the enterocele.

Diagnosis

The diagnosis of the large enterocele, especially following a vaginal hysterectomy, is not difficult. However, the differentiation between an enterocele and rectocele is sometimes extremely difficult. Waters,8 example, advocated the simultaneous vaginal speculum and digital examination. Meigs9 and others stress the importance of examining the patient in the upright position with the index finger in the rectum and the thumb in the vagina. No matter what method is used for diagnosis, many enteroceles will be missed unless the cul-de-sac is explored digitally when vaginal hysterectomies or vaginal plastic operations are done.

The cul-de-sac must be opened to explore it properly in performing the Manchester operation. This is best illustrated by Hill¹⁰ in his paper on 505 Manchester operations in which he noted that only 2 enteroceles were diagnosed preoperatively but 8 were recognized and repaired at operation. When the abdomen is open the cul-de-sac should be explored routinely. A prophylactic Moschcowitz procedure, or plication of the uterosacral ligaments, at this time might prevent future trouble.

The actual incidence of enterocele is difficult to determine, but Weed² gives it as 1 in 986 cases at the Ochsner Clinic and 1 in 1,168 from the Charity Hospital in New Orleans. Austin and Damstra⁴ state it is 2.16 per cent in their series of 73 cases out of 3,374 major gynecologic cases.

Surgical repair

Although various surgical attacks on enterocele had been described, notably those of Chomas¹¹ in 1885 and Marion¹² in 1909, it was not until the classic works of Mosch-cowitz¹³ in 1912 and Ward¹⁴ in 1922 that the correction of this particular hernia was formulated.

The Moschcowitz repair, like the Marion procedure, is a series of concentrically placed

Table IV. Operations employed in 123 patients with no previous operation

*	Emanuel	Good Samari- tan	Total
Vaginal hysterectomy Anterior and posterior colporrhaphies or Manchester operations	61	28	89
and enterocele repair Posterior colporrhaphy	6	12	18
and enterocele repair	10	5	15
Moschcowitz procedure	1	0	1
Total	78	45	123

purse-string sutures obliterating the cul-desac abdominally. The Moschcowitz repair in the past four decades has gradually been replaced by the Ward operation, but it has definite value as a prophylactic obliteration of a deep cul-de-sac in abdominal pelvic operation.

Ward's classic repair is a high excision of the enterocele sac vaginally with repair of the fascial defect utilizing the uterosacral ligaments. He used a sponge on an instrument in the rectum to orient the enterocele from the rectum. The "double-glove technique" with an index finger in the rectum is another method of orientating the operator in this occasionally difficult separation of enterocele from rectum. He described his method of enterocele repair with either retaining or removing of the uterus. Very little has been added to his basic surgical correction of enterocele. Ward's classic monograph should be read by all students interested in this field. His illustrations are simple and informative.

Another vaginal method of enterocele correction is the obliteration of the vagina by total or partial colpocleisis. Colpocleisis is not a popular method, as shown in Table VI, but, with it, in older women in whom intercourse is no longer desired there is less chance of recurrence, especially if previous repairs have been attempted. Certain operators have an abhorrence of this method.^{3, 5}

The method of surgical repair for an enterocele is determined by the following criteria: whether future coitus is desired,

Table V. Symptoms in 265* patients with enterocele

Symptom	No.
Prolapse	81
Draggy sensations	68
Rectal symptoms	51
Urinary symptoms	97
Bulging mass	97
Spotting or discharge	27

*Because these patients had one or more symptoms, the figures total more than 265.

whether more children are desired, whether the uterus is present or absent, and whether the approach is to be abdominal or vaginal for conditions other than the enterocele. With regard to the young woman in the childbearing age, enterocele with vaginal prolapse presents a problem. In this series there were 26 women (almost 10 per cent of the series) under the age of 40 years. This is a slightly greater incidence than Phaneuf³ reported and almost twice as many as Reed⁵ or Austin4 reported for this age group. A closer look at this group of 26 women under age 40 reveals that 13 had a vaginal hysterectomy; 7 had a Manchester operation; 5 had a vaginal plastic operation of some sort, and 1 had a Moschcowitz procedure. Of the 26 women under 40, 13 had 4 or more children; 9 had had 3 children; 3 had had 2 children, and I had had 1 child. Perhaps a Manchester operation would have been more suitable for this age group. Hill10 reported, in a series of 505 Manchester operations, 20 per cent of his patients were under the age of 40 years; 10 per cent had a complete prolapse. He felt that this operation was not adverse to future pregnancies, but that future deliveries should be by cesarean section to prevent recurrent genital prolapse. Solomons¹⁵ utilized the Manchester operation in 190 cases of uterine prolapse; 14 per cent of the patients he followed had children later. With the uterus already removed the vaginal approach was usually more applicable because of the better accessibility of the remaining fascial tissue so necessary for support. Occasionally, because of extremely poor tissue and/or previous vaginal operations, the combined abdominal and vaginal approach is necessary. Hardwic has a modification of the Moschcowitz operation which is used when the enterodle is associated with prolapse of the rectum. His modification is a denudation of the parietal peritoneum in the cul-de-sac and advancement of the rectum and sigmoid upward on the fascia and peritoneum about the sacrum. Incidentally, it is relatively common for an enterocele and prolapsed rectum to occur simultaneously, especially when the uterus has been removed.

Since many patients with enteroceles have associated anterior as well as posterior vaginal wall relaxation, it was not surprising to find that urinary incontinence was one of the chief complaints in this group of patients. With the recent advent of the Marshall-Marchetti operation and its abdominal approach to the correction of the anterior vaginal wall, it is conceivable that there may be a renaissance of some form of the Moschcowitz procedure. Burch17 recently noted that enterocele was the most common complication after an abdominal urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse. He advocates an associated Moschcowitz operation to prevent this complication. Anatomically, the emphasis for various utilization of the uterosacral ligaments has been the keystone for enterocele repair. Many authors have emphasized this. Among them are Reed,5 Hiller,18 and Harrison and McDonagh. 19

McCall,²⁰ Torpin,²¹ and Waters²² have emphasized the use of culdoplastic technique for enterocele correction and prevention. They attempt to remove the redundancy of the cul-de-sac by imbrication or excision.

For the past decade more emphasis has been directed to preventing recurrence of enteroceles as well as to curing them at the time of operation. The critical weakness in the pelvic floor repair is between and below the uterosacral ligaments and the upper part of the levator ani muscles. Harrison and McDonagh, 19 Hiller, 18 and Shaw²⁸ recognized this. In 1951 Shaw published an article

emphasizing a bold exposure of this area. He does this by dissecting the posterior vaginal wall from the posterior fourchette up to the back of the cervix or the neck of the closed enterocele sac. Here the downward prolongation of the uterosacral ligaments are found laterally as they run into the "ground bundles" of the endopelvic fascia. The levator ani muscle with its fascial investments are visually identified and the fascia is cut

parallel to the muscle and stripped medially where it meets the fascia on the superior portion of the levator muscle. Joined in the midline these fascial strips give good support to this normally vulnerable area.

This levator fascia shelf has an inclination of 30 to 45 degrees to the levator muscles. An opening two fingerbreadths wide can be left between the levator muscles for an adequate functional vagina above the level of

Table VI. Procedures used for correcting enteroceles

	Emanuel	Good Samaritan	Total
A. Vaginal hysterectomy and enterocele repair	72	32	104
3. Manchester operation	14	13	27
Anterior and posterior colporrhaphy	25*	10†	35
Anterior colporrhaphy	1	0	1
Posterior colporrhaphy	34	17†	51
Amputation of cervix	2	0	2
Amputation of cervix and anterior colporrhaphy	1	0	1
Ward operation (enterocele repaired alone)	1	0	1
C. Obliteration of vagina and enterocele repair			
Colpocleisis	1	2	3
Colpocleisis and posterior colporrhaphy	2	3	5
LeForte operation	4	2	6
D. Abdominal correction			
Moschcowitz	5	1	6
E. Miscellaneous operations with enterocele repair also			
Partial vulvectomy	1	0	1
Fundus of uterus to coccygeal ligament	1	0	1
Anesthesia and vaginal packing	0	1	0
Total	180	85	265

^{*}Also Shaw operation.

Table VII. Procedures used in conjunction with enterocele repair in four series of reported cases

	Weed	Reed	Phaneuf	Kinzel
A. Vaginal hysterectomy	4	11	13	104
B. Vaginal plastic operation	12	0	0	0
Manchester operation	0	93	0	27
Plastic with sac obliterated	3	0	0	100
Vard operation	19	48	66	20
nterposition	3	0	0	0
imputation of cervix	3	0	0	0
C. Abdominal approach	0	11	10	6
Combined abdominal and vaginal	1	4	0	0
D. Vaginal obliteration	0	0	0	0
Colpocleisis	3	0	2	8
E. Miscellaneous operations plus enterocele repair	0	0	0	3
Total	52	167	91	265

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[†]Also abdominal hysterectomy.

the levator muscles. This procedure produces a vaginal vault placed back near the rectum and increases the oblique angle of the vagina through the pelvic floor with maximum strength and length.

Some authors disagree with suturing the levator ani muscles together as they feel that causes pain and later constriction of the vagina with dyspareunia.²⁴

Hundley²⁵ invaginated the enteroceles and attached the invaginated end securely to the fundus anteriorly.

If the uterosacral ligaments were always well developed and firm, their approximation and anchoring high behind the uterus, if present, or to the posterior part of the imbricated paravesical fascia shelf would suffice. However, the uterosacral ligaments are often thin and frayed-out, and they vary from woman to woman. Some uterosacral ligaments are only thin folds of peritoneum. Campbell,26 in an anatomic study of the uterosacral ligaments, found that the distal or sacral portion of the uterosacral ligaments were much weaker than the anterior or uterine portion. Thus, it is obvious that the pressure of difficult or repeated childbirth would probably injure the weak portions of the uterosacral ligaments more, and in a patient with previous hysterectomy the strong portion of the uterosacral ligaments would be removed, thus stretching the distal portions more.

Austin⁴ used fascia lata to purse-string suture this weak area. Shaw's and Austin's techniques are especially helpful where previous operation has destroyed the fascial tissue. (As shown in Table VI there were a

Table VIII. Procedures selected in 4 series of reported cases

	Weed (%)		Phaneuf (%)	Kinzel
Vaginal hys- terectomy	7.7	6.5	14.7	39.2
Vaginal plastic operation	77	84.5	72.6	52
Moschcowitz operation	2	9	11	2.3
Vaginal oblitera- tion	13.6	0	2.2	5.3

number of various combinations of procedures done.)

Techniques used in present series contrasted with others

In this series, vaginal plastic operations in association with enterocele repair were done in 52 per cent of the cases. Next in frequency were enteroceles repaired during vaginal hysterectomies (with plastic procedures). This was done in 39.2 per cent of the cases. Colpocleisis and other vaginal obliteration procedures were done in 5.3 per cent of the cases. The Moschcowitz operation was done only six times, or in 2.3 per cent of the cases.

Comparison of our procedures with those of other authors (Tables VIII and IX) reveals a much higher incidence of vaginal hysterectomy and enterocele repair and subsequently less with vaginal plastic procedures.

Reed, who had the lowest incidence of vaginal hysterectomies, admits that perhaps his incidence was too low. He felt that the Manchester repair in his hands gave a more stable repair than a vaginal hysterectomy.

The Moschcowitz procedure was very seldom done as a corrective method in this series and surely could have been utilized more frequently, as it was by Reed and Phaneuf.

Vaginal obliteration was used in 5.3 per cent of the cases in this series and was abhorred by Reed and Phaneuf, while Weed used it in 13.6 per cent of his cases (Table X).

From this study it is apparent that there are many methods and combinations of vaginal plastic operations used for the correction of enteroceles. All methods should be at least known and a good knowledge of pelvic surgical anatomy is a must for correction of this defect. It is surprising that no use of fascia lata as suggested by Austin⁴ was made.

Conclusions

1. No revolutionary ideas of surgical repair of the enterocele have been added since

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2. Recent authors have emphasized that the uterosacral ligaments alone give inadequate support for an enterocele repair.

3. The cul-de-sac must be opened to be

explored in vaginal plastic procedures to detect latent enteroceles.

4. Abdominal hysterectomies or suspension operations in women with prolapse of the uterus often may lead to future enterocele formation.

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Discussion

Dr. Donald Thorp, Seattle, Washington. A useful examining technique for the revelation of enterocele consists of inserting one index finger in the rectum while using 2 fingers of the opposite hand in the vaginal vault. Examination of the cul-de-sac when the pelvis is opened abdominaily should be routine.

in the correction of enterocele, once the sac has been properly dealt with as in any true hernia, reliance upon approximation of the sacrouterine ligaments alone is inadequate. The M schowitz technique is but a gesture impelled more by hope than by anatomic reasoning.

Dr. Kinzel does well to bring out Ward's technique of using the levator fascia. In 1959, Dr. Ralph Benson emphasized the use of the cardinal ligaments as well as the joining the saccouterine ligaments for the elimination of future weakness in this area. He incidentally cautioned against use of heavy suture material.

One of the outstanding contributions from Dr. Kinzel's dissertation is the warning that we

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must be alert for the discovery of such coincidental defects as enterocele. If the surgeon repairs the bladder and rectal supports but leaves a hernia in the vaginal vault he is guilty of mediocrity as well as of negligence.

Dr. Ralph L. Hoffman, San Diego, California. How many have seen a ruptured enterocele? In San Diego several years ago I saw a woman, in the operating room, who had previously had vaginal repair, and evidently an enterocele which had been overlooked. Just prior to admission she had squatted down to look at a cake in the oven, had felt a popping sensation, and out had come a large mass of bowel. The neighborhood physician confronted with this problem copiously applied penicillin ointment, wrapped the mass in a bath towel, and sent the woman to the hospital. It took an hour and a half to clean the fuzz off the bowel. At laparotomy we were able to pull the intestine back through the ruptured enterocele. We closed the enterocele from above and it has remained cured.

Another complication of enterocele was observed in a patient near term during pregnancy. The patient had a large enterocele, and from pressure of the baby's head against it in the pelvis she developed an obstruction of the small intestine. This was relieved by pushing the baby's head up, reducing the enterocele, and delivering the baby. The enterocele was repaired at a later date.

Dr. John R. Upton, San Francisco, California. I should just like to stress the following adequate preoperative measures:

1. A detailed history is mandatory; a minute pelvic and a vaginal examination is a must.

Malignant growths must be ruled out by cytology and biopsy studies.

3. Traumatic lesions, acute or chronic, with distortion of the normal anatomic landmarks, should be carefully noted, or the ureter studied to see if it is distorted by adhesions. Is it advisable to pass ureteral catheters? Should a barium enema study be preformed?

4. Infectious conditions must be treated and cured prior to operation.

5. Hormonal deficiencies with local manifest tions must be corrected; this is particularly necesary for the senile type of vaginal mucosa.

 Allergic manifestations require study and removal of the offending substance prior to operation.

DR. KINZEL (Closing). Ureteral cathete's should be passed before an enterocele sac is repaired. This will aid in their identification, especially if it is necessary to ligate the sac blindly inside the peritoneal cavity.

Preoperative retrograde pyelograms would also be a safeguard to determine previous injury or displacement of the ureter.

I do not believe a barium enema, as a rule, would aid the physician very much in enterocele diagnosis.

George Gray Ward, who did not overlook very much in enterocele repair, suggested a sponge on an instrument to orient the rectum from the enterocele sac. A "double-glove" technique with the operator's finger in the rectum also occasionally aids the surgeon in a difficult dissection of the enterocele from the rectum.

Management of early carcinoma

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OVER the past decade we have gradually crystallized our thoughts concerning the diagnostic criteria and therapeutic methods employed in the management of early superficial carcinoma of the cervix. During this period our ideas on this subject have changed materially. We have refined our diagnostic techniques, have extended the scope of the diagnosis, and have substantially altered our methods of definitive therapy. The significance of the extent of the lesion and its influence on management has taken on more meaning. As a result of this experience, we would now manage many patients with restricted lesions quite differently than we did in 1950.

Across the country there exists some difference of opinion concerning the choice of cold conization or representative multiple biopsies in making the diagnosis of a restricted cervical cancer. There is a considerable difference of opinion in establishing the limits to which superficial lesions may extend past the surface and still be classified as something less than a frankly infiltrative cervical cancer. It is, thus, not surprising that there is also some difference in the criteria governing the extent of therapy. These con-

siderations have been reviewed in previous publications from this department.^{1, 2}

Generally, early subclinical cancer is detected by vaginal cytology examination or by a biopsy from a nonspecific cervical lesion. It has been our feeling that an adequate cold conization will best delineate the extent of the lesion and that prior staining of the cervix with Schiller's iodine solution is very helpful. In addition, the conization procedure will often serve as definitive therapy. The patient is usually found to have a suspicious epithelial atypism, an intraepithelial carcinoma, a carcinoma with limited or questionable stromal invasion, or occasionally a frankly infiltrative cancer.

Most would agree that the suspicious epithelial atypism has been sufficiently treated by the conization. Since the malignant potentialities of the untreated atypia have been documented,³ it is important that careful follow-up be effected. The patient with frankly infiltrative cancer usually presents little problem with regard to the choice of therapy and should have the full treatment that this disease requires. However, the patients with intraepithelial restriction of the cancer and those with delimited and restricted stromal invasion present the possibility for some variation in treatment depending on the exigencies of the individual case.

Prior to 1954 we had treated all patients with endocervical gland involvement, questionable stromal invasion, or restricted

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Presented at the Twenty-seventh Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society at Yosemite, California, Sept. 29-Oct. 1, 1960. stromal invasion by full irradiation or by hysterectomy and pelvic lymphadenectomy. The only exceptions were pregnant patients in whom the diagnostic criteria were thought to be open to question. Since routine cytologic screening was uncovering a substantial number of such cases, it soon became apparent that this restricted involvement was not accompanied by parametrial or lymph node involvement. Indeed, it was very often impossible to demonstrate residual carcinoma in the hysterectomy specimen following conization. It seemed debatable, therefore, that the risks of radical therapy and its attendant morbidity were justifiable in these patients.

Since 1954 cases of squamous cancer with this restricted degree of involvement have been placed in the Stage 0 category. This classification in our hands includes all microscopic, superficial carcinomas of the cervix which are confined to the surface epithelium, the endocervical glands, and/or the subjacent 2 to 3 mm. of stromal tissue. For purposes of management each case was individualized and treated either by restricted radiation, extrafascial (but not radical) total hysterectomy, or by conization alone.

This study was instituted to review our experience and evaluate the immediate results of our methodology in the management of delimited superficial cervical carcinoma. Our present policy of management has not been in force long enough to make a significant 5 year assessment.

Material and methods

Two hundred and eighty-five patients from the Obstetrical and Gynecological services of the UCLA, Harbor, and City of Hope Hospitals have been included in this report. All were studied during the period 1950 to 1960 by cervical conization in the investigation of cervical cancer. The great majority of cases were detected by routine vaginal cytology and most of the patients had no suggestive symptoms or distinctly suspicious lesions. Their ages ranged from 19 to 87 years with the largest group falling in the age decade 30 to 39. The parity of the group

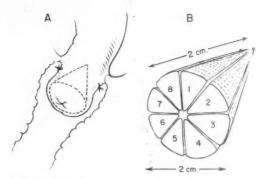


Fig. 1. Conization specimen indicating preparation of serial blocks.

varied between 0 and 16 with the largest numbers comprising the para ii and para iii groups. Thirteen per cent were nulliparous and 12 patients were pregnant when the conization was carried out.

Following positive or repeated suspicious vaginal cytology, or following a biopsy indicating intraepithelial carcinoma, the patients were subjected to cervical conization. In general the conization was carried out with a No. 11 Bard-Parker scalpel blade and an attempt was made to remove a specimen measuring at least 2 cm. in diameter across the varginal portio and 2 cm. in depth (Fig. 1). In the majority the cone was larger and in some cases it measured 5 by 3 cm. In other instances, especially in elderly women whose cervices were small and flush with the vaginal vault, it was difficult to obtain a cone specimen of these adequate dimensions. It was considered helpful to use hemostatic sutures placed in the lateral substance of the cervix high up in the lateral fornices. Used as guy wires, these sutures were useful in maintaining exposure. Following the conization, the cervix was dilated and a fractional curettage was performed. In most cases the cone site was left open following suture hemostases but very often the cervix was reepithelized in the manner of Sturmdorf.

After fixation in Zenker's formol solution the specimen was serially blocked into at least 12 to 14 portions with care being exercised to orient the block surfaces properly during the embedding procedure. Supsections were taken throughout each block.

The total number of sections taken depended in large part upon the diagnostic problems suggested by the initial sections from each block.

When the review of the conization sections was completed the decision concerning further management of the case was made. The patient was either followed, subjected to total hysterectomy, or given irradiation therapy. When frankly infiltrative carcinoma was found or if lymphatic channels were seen to be involved in the cone specimen, a radical hysterectomy and pelvic lymphadenectomy, or full cancerocidal irradiation was carried out.

If hysterectomy was elected following the conization it was usually performed 3 to 6 weeks after the conization. If done later, it was usually because positive cytology or a change in the patient's circumstances dictated abandoning the conservative management. In any case the cervical portion of the hysterectomy specimen was completely blocked and a careful search made for residual carcinoma. In all cases whether followed by cone alone or subjected to hysterectomy, the patients were registered with the follow-up secretary to insure continued surveillance.

Results

Investigation of the conization specimens in the prescribed manner revealed the tissue diagnoses as summarized in Table I.

It will be noted that 28, or 10 per cent, of the patients who required conization for the proper assessment of their lesion were found to have frankly invasive cancer. Many

Table I. Tissue diagnoses on conization specimens

Pathological diagnosis	No.	%
Infitrative carcinoma	28	10
Carcinoma with microscopical		
avasion	68	24
Intraepithelial carcinoma	88	31
Suspicious squamous atypia	37	13
Chronic cervicitis, reserve cell		
hyperplasia, etc.	64	22
Total	285	100

of the patients in this group did have an early but nonspecific lesion and conization was performed to clarify equivocal punch biopsies. The group also includes some patients in whom the cone appeared to clear the lesion quite well but the pattern of the neoplasm was that of an infiltrative carcinoma. By and large, this group presented little problem in diagnosis from the cone specimen and the therapy was carried out as prescribed for a Stage I carcinoma of the cervix (Table II).

Approximately 1 out of 5 of the patients coned were revealed to have no suspicion of a malignant neoplasm. Many of the patients in this group had negative vaginal cytologic examination and conization was performed to evaluate an equivocal biopsy or a suspicious Schiller-positive (nonstaining) cervical lesion. Three such patients were subjected to hysterectomy; 1 abdominal hysterectomy for myomas of the uterus and 2 vaginal hysterectomies for procidentia.

The suspicious squamous atypias were severe aberrations showing neoplastic tendencies which, however, did not meet the criteria for intraepithelial carcinoma. Most showed a dysplasia which did not extend throughout the entire thickness of the epithelium. Benign-appearing atypia such as reserve cell hyperplasia (epithelial prosoplasia) were not included in this class. However, in many instances it was noted that reserve cell hyperplasia was closely associated with intraepithelial and early invasive carcinoma. Four of these patients with suspicious squamous atypia have been subjected to hysterectomy for other gynecological conditions and the rest have been followed with periodic vaginal cytology. It is noteworthy, in view of the reported malignant potential of this lesion,3 that none of these patients treated by conization has had a recurrence so far or shown progression to intraepithelial cancer.

The largest group in this series consisted of patients with intraepithelial squamous carcinoma. These lesions were occasionally confined to the surface epithelium of the cervix but often involved the endocervical

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Fig. 2. Intraepithelial carcinoma involving and presumably replacing endocervical glands.

glands (Fig. 2). This group also included those cases in which stromal invasion was suggestive but not definite. In many cases it was impossible to discern with certainty whether stromal invasion had, indeed, taken place. In these cases it was difficult to evaluate the basal alignment of cells or detect the presence of a delimiting basement membrane. As previously reported, it was sometimes not possible to determine whether a nest of carcinoma cells had completely replaced an endocervical gland or had invaded en masse into the stroma just below the surface epithelium. In cases of doubt those with only questionable invasion were placed in the intraepithelial carcinoma group. As a matter of actual practice this distinction may prove to be of only academic importance.

Sixty-eight cases satisfied our criteria for superficial or restricted microinvasive squamous cancer. These lesions were truly microscopic. The neoplastic change involved the surface epithelium or that of the endocervical glands with invasion extending into not more than the subjacent 2 or 3 mm. of stroma (Fig. 3). No patients were included in this group if the histological pattern of the neoplasm was that of an infiltrative carcinoma or if lymphatic channels were involved even though the lesion was superficial and well cleared by the cone. These superficial lesions with restriction or microinvasion of the stroma were for purposes of therapy classified as Stage 0 cervical cancer along with the truly intraepithelial cancers.

Of the 156 patients classified as having Stage 0 cervical cancer, 19 per cent were treated by conization alone (Table III). This figure is somewhat misleading since 10



Fig. 3. Superficial microinvasive cervical cancer. The lesion was delimited within the cone and restricted to a depth of 2 to 3 mm. subjacent to the surface epithelium.

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of these patients refused operations or were considered poor surgical risks. It was actually elected to treat only 20 patients by conization and careful follow-up. The majority of these were in their twenties or wished to preserve their capacity to bear children. The 9 patients treated by irradiation were either poor risk patients or postmenopausal.

Hysterctomy was the niethod of treatment in 75 per cent of the Stage 0 cases. Generally, it was performed as an extrafascial procedure with a wide vaginal cuff (2 cm. or more) and with preservation of the ovaries. Thirty per cent of the specimens showed residual cancer in the uterus following conization. This figure is consistent with other reports.4 An additional 7 per cent showed various squamous atypias but these changes were difficult to assess in the recently healed cone sites.

It is possible and it seems feasible to break down the 30 per cent residual cancer rate into figures which have more meaning in the individual case. When study of the conization sections was extended to assess clearance of the neoplasm at the edges of the block, the residual cancer figures appeared more determinate (Table IV).

When the lesion appeared cleared by the conization, only 3 of 46 of the subsequent hysterectomy specimens revealed cancer. If the lesion was not cleared, this finding rose to 45 per cent. Most of the uncleared lesions extended off the upper (endocervical) end of the cone. Occasionally the cone would not clear the lesion at either end and rarely would the ectocervical portion of the lesion alone extend past the cone.

Table V indicates that patients with superficially invasive cancer were less apt to have their lesions designated as "cleared" b) the cone (22 per cent), than those with intraepithelial cancer (56 per cent). This deference probably results from the superficial invasion diagnosis being associated with the more extensive lesions. It is noteworthy that, whereas 59 per cent of the · Stage 0 cones could not be designated as having cleared the lesion, only 30 per cent

Table II. Management of Stage I cervical cancer following conization with findings in hysterectomy specimens

Irradiation therapy			12
Radical hysterectomy and pelvic			
lymphadenectomy			16
No residual cancer in specimen	5	(31%)	
		(69%)	
Lymph node involvement	0	, , ,	
Total			28

Table III. Management of Stage 0 cervical cancer following conization with finding in hysterectomy specimen

Treatment			No.	%
Follow-up only			30	19
Irradiation			9	6
Hysterectomy			117	75
Residual cancer	35	(30%)		
No residual cancer	82	(70%)		

showed residual cancer in the uterus following conization.

Comment

The assessment of early subclinical cervical cancer requires adequate conization before a proper diagnostic evaluation can be made. Cervical conization, as a hospital procedure with systematic study of the specimen, is necessary to rule out frankly infiltrative cancer so that a nonradical form of treatment can be carried out.

It may be impossible in many instances to make the differentiation between truly intraepithelial squamous cancer and superficial, microinvasive cancer. Indeed, the distinction may prove not to be important if the cervix is adequately evaluated. Earlier experience with these lesions and the increasing number subsequently detected with the aid of routine vaginal cytology has influenced us to group these equivocal lesions together for purposes of management. Stage 0 cervical cancer would seem an appropriate designation for this group. The names does not connote an epithelial restriction which is sometimes impossible to affirm and it is a simple designation of international recognition.

Table IV. Correlation of apparent clearance of lesion by cone with finding of residual cancer in hysterectomy specimen in Stage 0 cervical cancer

Apparent clearance of lesion by cone	Residual cancer in hysterectomy specimens	No cancer in hysterectomy specimens
Cleared		
Microinvasive cancer	. 1	14
Intraepithelial cancer	. 2	29
	3 (6.5%)	43 (94.5%)
Clearance not demonstrated		
Microinvasive cancer	18	21
Intraepithelial cancer	14	18
	32 (45%)	39 (55%)

Table V. Correlation of apparent clearance of lesion by cone with extent of neoplasm in Stage 0 cervical cancer

Extent of malignant	Lesion de- limited by conization		Lesion not delimited by cone		
change	No.	%	No.	%	Total
Microinvasive cancer	15	22	53	78	68
Intraepithelial cancer	49	56	39	44	88
Total	64	41	92	59	156

Stage 0 cervical cancer does not present serious problems in management once the proper diagnostic evaluation has been made. Simple total hysterectomy, irradiation restricted to the cervix, or conization alone are all effective methods of treatment consistent with the individual circumstances. If, however, the definitive treatment is restricted to conization alone, adequate follow-up including vaginal cytology must be assured. Treatment by conization has a definite place in the management of women who are young or who hope to bear children later.

The over-all finding of 30 per cent residual cancer in the hysterectomy speciment following conization evokes pause in allowing these patients to proceed without hysterectomy or radiation. In contrasts, the accuracy of vaginal cytology and the relatively slow or occasional regressive development of this lesion gives us the confidence to follow these women without further definitive therapy other than the conization.

Proper evaluation of the cone specimen may help in the decision concerning further treatment. Accurate determination of the limits of the lesion within the cone would seem to change the 30 per cent chance of residual to one which is less than 10 per cent or more than 40 per cent according to the apparent clearance. It is true that the inability to find a microscopic residual of cancer does not mean that the uterus is free of cancer; study of the hysterectomy specimen may miss a focus of residual cancer.

On the other hand, a prospective approach to the study of the conization specimen with respect to clearance of the lesion would seem essential. The inability to demonstrate residual cancer in 55 per cent of the cases in which the cone sections did not demonstrate clearance indicates the caution with which a designation of clearance was made (Table IV). This designation could be made with more confidence (and presumably with more accuracy) in a prospective study wherein the blocks were cut and embedded with a major interest directed toward assessing clearance.

Generally, it should be emphasized that the preferred definitive therapy of Stage 0 cancer is total, extrafascial hysterectomy or occasionally local irradiation of the cervix. If there is good reason for preserving child-bearing function or if the patient is young, consideration should be given to instituting no further therapy other than the conization. It is not an emergency decision but adequate follow-up must be assured. Thorough evaluation of the cone specimen is indeed helpfoly, and further biopsies or even another conivation at a later date is not entirely impractical in a young woman.

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Summary

- 1. Two hundred and eighty-five patients suspected to have early, usually subclinical cervical cancer were subjected to cervical conization.
- 2. Systematic investigation of the conization specimens revealed 28 infiltrative cervical cancers, 156 intraepithelial or superficially invasive (microinvasive) cancers, and 37 severe squamous atypias.
- 3. The superficially invasive cancers (68 patients) were grouped with the truly intraepithelial cancers as Stage 0.
- 4. Seventy-five per cent of the Stage 0 cancers were treated by total hysterectomy.

Residual cancer was demonstrated in 30 per cent of the hysterectomy specimens.

- 5. If during investigation of the cone, the Stage 0 lesion was assessed to be cleared, residual cancer could be found in only 6.5 per cent of the hysterectomy specimens. If the lesion was not designated as cleared by the cone, 45 per cent residual cancer was demonstrated.
- 6. Conization, as such, has a definite place in the management of young women with Stage 0 cervical cancer. This restricted treatment should only follow a thorough diagnostic evaluation and should be undertaken only if adequate follow-up surveillance can be assured.

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Discussion

Dr. C. F. Fluhmann, San Francisco, California. I have recently analyzed a series of 50 patients with Stage 0 carcinoma from both the clinical and pathological aspects. Without going into details, there are two findings which I should like to mention as they emphasize various points brought out by Dr. Moore. In the first place, almost half our patients showed no grossly recognizable lesions of the cervix and the only reason that a cone biopsy was performed was because of a persistently positive vaginal smear. Second, a study of the step sections of the cervices showed that the carcinoma in situ in most cases was present not on the ectocervix but in the canal. Thirty-six in situ cancers involved either the transitional zone or the canal or both. Only 14 extended over the portio and, of these, 12 were also present in the canal or the transitional zone.

These 2 observations in our small series indeced Dr. Harold Lyons and me to give serious thought to the problem of diagnosis and we concluded that simple biopsies of the portio have little place in the management of these patients. We believe that a biopsy of the portio is indicated only when there "are grossly suspicious lesions. On the other hand, when positive smears

have been obtained a cone biopsy should be done (1) when gross lesions are not seen on the ectocervix, (2) when there are repeated positive smears and biopsy of the portio has not shown the presence of malignancy, and (3) when a carcinoma in situ of the portio has been demonstrated in a biopsy specimen, obviously in order to eliminate invasion at a higher level.

Although I am in complete agreement with Dr. Moore regarding his clinical conclusions, I do have some reservations on some of his pathological interpretations. It is quite wrong to speak of "gland involvement" or "gland invasion" for the simple reason that there are no glands in the cervix in the sense of tubes coursing down from the surface, the classic so-called compound racemose gland. Instead, the cervical mucosa is made up of a complicated pattern of clefts and tunnels. The photograph in his Fig. 2 is not of a racemose gland running from the top down but of tubular channels which extend horizontally to the surface and when followed by adequate numbers of serial sections they will be shown to connect with a cleft or groove of

The connotation "reserve cell hyperplasia" as a pathological diagnosis is most unfortunate and should be abandoned. It actually refers to a normal constituent of the cervical mucosa and is found at all times from intrauterine life to old age. It also has been called epidermization, metaplasia, and squamous prosoplasia. It occurs especially in the transitional zone between the columnar epithelium of the canal and the squamous epithelium of the portio. I am certain that many mistakes have been made because this histological transformation has been interpreted as a pathological change and not recognized as a normal finding. It is particularly significant be-

cause carcinomatous changes most often $t\epsilon \, ke$ place in the transitional zone.

DR. MOORE (Closing). I agree thoroug ly with Dr. Fluhmann about gland replacement or gland involvement. We cannot tell in every case what an extension into the stroma represents. It may be a cleft, it may be a replacement of the "gland," and it may be a partial involvement of the gland. I did mention the fact that I did not think we could make this designation accurately in all cases.

OBSTETRICS

Physiologic or dysfunctional incompetence of the cervix

Diagnosis and surgical treatment in the nonpregnant woman

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The problem of incompetence of the cervix and its relation to pregnancy has excited a great deal of interest throughout the medical world. Incompetence of the cervix is an entity during pregnancy, the diagnosis and repair of which have been demonstrated by Shirodkar¹ and has been modified by Barter and associates,² Durfee,³ and Baden and Baden⁴ in this country and by Green-Armytage and co-workers,⁵ McDonald,⁶ Palmer and associates,²-10 and Mey¹¹ in Europe. Our particular interest has been centered in the diagnosis and treatment of this condition in the nonpregnant woman.

There are at least three types of cervical incompetence. 10, 12, 13

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The radiopaque medium used in this study (Special Salpix) was provided by the Ortho Company, Raritan, New Jersey.

1. The most common is the structural type, which is usually traumatic in origin from the loss of tissue as the result of placenta previa, lacerations extending to the internal os at delivery, or too vigorous dilatation and/or curettage of the region of the internal os. The structural type of incompetence should also include those cases in which the internal os of the cervix is distorted by a loss of continuity because of defects of the lower uterine segment such as fibroids and other new growths.

2. The second is the congenital type, always associated with primary habitual abortion. This group of cases should include such developmental abnormalities as bicornuate and other similarly congenitally deformed uteri.

3. The third type of incompetence is classified as physiologic or dysfunctional incompetence. In this type there is no defect of the internal os that is palpable or demon-

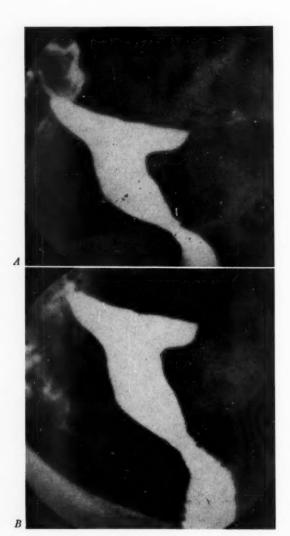


Fig. 1. Normal. A, Before enzyme; B, after irrigation with enzyme.

strable by the usual investigative methods. In this group the cervix remains competent to balloons and dilators and by the usual radiographic techniques appears quite normal. This last type of incompetence is the subject of this report.

Physiologic or dysfunctional cervical incompetence is demonstrable by the techniques reported by the senior authors in 1955¹³ and 1957.¹⁴ As was reported, the authors' interest was stimulated by the dramatic, consistent changes shown by cervicohysterosalpingography when the enzyme, bromelain, was used to irrigate the vagina and cervical canal. The procedure is

always carried out at the estimated time of ovulation. It has been our feeling that tubal obstruction demonstrated by hysterosal-pingography at a time other than ovulation may be false, and the study should be repeated on the proper day.

No other patient preparation is used in our studies, except to have the patient void just before the procedure. With a DeVilbiss vaginal speculum the cervix is exposed and grasped laterally with single-toothed tenacula and the cannula is inserted. This cannula was devised by the authors14 and consists of a straight cannula with a Foley catheter type balloon supported by a spherical cup. The cervical end of the cannula projects about 1 cm. beyond the balloon and just enters the cervical canal. A watertight seal is obtained with countertraction by the tenacula pulling the cervix against the air-filled balloon. This permits visualization of the cervical canal as well as the uterine cavity and tubes. A 10 c.c. syringe filled with medium is previously attached to the cannula. After removal of the speculum, the patient is properly positioned on the fluoroscope table, and media is slowly injected. The filling is observed fluoroscopically for momentary periods and spot films exposed as indicated. When satisfactory visualization of the tubes or peritoneal spill of the media is accomplished, the cannula is withdrawn and the vagina is irrigated with bromelain solution. The solution is allowed to remain in the vagina for 3 to 4 minutes. The vagina is then dried with sponges and the cannula reinserted. More media is injected and the fluoroscopy is repeated, with further films taken as needed to demonstrate changes.

In the normal patient whose cervix is competent, the constriction ring is easily visualized (Fig. 1, A). Minimal relaxation occurs after irrigation with enzyme solution in many patients, as shown in Fig. 1, B. This is considered normal. The structural incompetence is illustrated in Fig. 2. This defective internal os was caused by a placental previa. Enzyme irrigation does not change the degree of relaxation in this group of

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patients. Congenital incompetence is illusrated by Fig. 3. The incompetence illusrated is not affected by the use of enzyme. Physiologic or dysfunctional incompetence is not apparent on the primary salpingograms. In fact, most of these patients show what is apparently a normal internal cervical os (Fig. 4, A). The dramatic change which takes place when the cervix is irrigated with bromelain is shown by Fig. 4, B. The incompetence shown in this illustration is evident. Only those patients with a history of abortion of a fetus older than 15 weeks showed relaxation of the internal os of sufficient degree that a diagnosis of incompetence could be made.

The usual history is that of one or more term or near term deliveries followed by midterm abortions of every subsequent pregnancy. Those patients in whom there was demonstrated the characteristic dilatation of the internal os and who have refused surgical correction have had spontaneous abortions of all their subsequent pregnancies, as they had previously, at 15 weeks or later. One patient with only moderate changes, according to our standards, carried to near term but only with great difficulty.

Our first three attempts at repair were by the method described by Lash and Lash. 15 This method of repair is used primarily for those patients who show a defect in the continuity of the internal os demonstrable by hysterosalpingograms. A wedge of the cervix is excised and the defective portion is reinforced. This method is inadequate for patients with physiologic or dysfunctional incompetence. Two of the 3 patients became pregnant and lost their babies at 16 weeks. One of these 2 patients was subjected to operation again, namely cervicoplasty with utilization of a cutis graft. Term delivery of twins followed the repair. The case history is given in detail below.

The material for this report was composed of 147 patients. Physiologic or dysfunctional incompetence of sufficient degree to recommend operation occurred in 24. Of these 24 patients, 15 refused operation. Five of them subsequently became pregnant and have



Fig. 2. Incompetent internal cervical os following placenta previa. This deformity remains the same after irrigation with enzyme.



Fig. 3. Congenital cervical incompetence which remains the same after irrigation with enzyme.

had abortions of one or more pregnancies at 15 weeks or later, and none of them carried beyond 24 weeks. Nine patients have been subjected to repair with cutis grafts. Pregnancy has occurred in 7. Six of these have been delivered of 11 living infants at or near term. Two of these patients have had abortion, 1 with villous fibrosis at 12 weeks and the other with amnionitis (see case report). All of these patients underwent cesarean section near term except one who was delivered vaginally elsewhere. She has had 3 term vaginal deliveries. The first one after the repair was accompanied by bleeding from a lacerated cervix, but the two

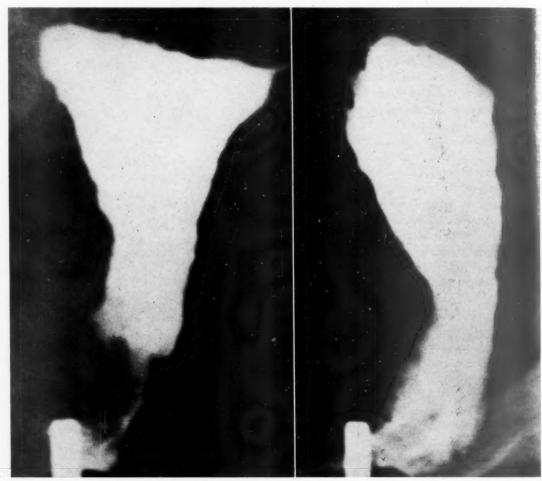


Fig. 4. Physiologic or dysfunctional incompetence of the internal os. A, Before enzyme; B, after enzyme.

subsequent ones were essentially normal. Twins occurred once in the series.

The operation

One buttock is prepared and a strip of skin 2 to 3 cm. wide and 15 cm. long is denuded with a dermatome. The cutis is then excised, the wound edges sutured, and the epidermis reapplied. The strip is cleaned of all fat from its undersurface and placed in saline for later use.

The patient is placed in lithotomy position and the cervix brought down with a tenaculum. Dilatation and curettage is performed in the usual manner.

The cervix is then circumcised at the

junction of the vaginal portio and the vaginal mucosa. The vaginal mucosa is dissected from the cervix up to the level of the internal os. A wedge of approximately one fourth of the total circumference of the cervix and extending from the external os to the internal os is excised (Fig. 5).

The cervix is then reconstructed. Chromic No. 2-0 sutures are used for the innermost layer. They are placed at intervals of about 1 cm. and care is exercised that the mucosa is inverted into the canal. The middle layer (No. 0 chromic) is placed at intervals of 1.5 cm., the larger suture being used to help produce more fibrosis and scarring. The outer layer (No. 2-0 chromic) is placed at

intervals of 1 cm., approximating very acurately the vaginal portio particularly Fig. 6).

The previously prepared cutis graft is then applied beginning at the level of the internal os and is sutured in place at intervals of 1.5 to 2 cm. The graft should be tightly applied that the possibility of collection of serum or blood beneath it is minimized. The result is a tight spiral which encircles the cervix about three full turns (Fig. 7). The vaginal mucosa must then be tightly applied to the graft with interrupted sutures. The resultant canal should take a No. 7 Hegar dilator with ease. Postoperatively, an antiseptic vaginal cream is used until healing is complete.

Salpingograms are repeated 3 months later and should show no dilatation when the cervix is irrigated with the enzyme.

Case reports

Case 1. Mrs. A. M., a 35-year-old Japanese housewife and clerk for a government agency had been pregnant four times. The first baby was delivered at 8 months in 1951 and died within a few days of birth. In 1952 the patient had a spontaneous abortion at 16 weeks. This was followed by dilatation and curettage. In 1953 an abortion at 20 weeks occurred, and in 1954 an abortion occurred at 18 weeks.

The patient was found to be an essentially normal woman with a normal menstrual cycle and a normal pelvis, except for gaping of the external os of the cervix. Cervicohysterosalpingograms showed sufficient change and relaxation that a diagnosis of physiologic incompetence of the internal os was made, and the patient underwent a repair of the cervix by the method of Lash and Lash. 15 Postoperatively, the lowermost vaginal portion 'showed gaping by breakdown of about 1.5 cm. and had the appearance of an anterior laceration. This was repaired sucessfully 3 months later.

The patient soon became pregnant, and at 16 weeks the above sequence of events again occurred. The cervix dilated painlessly and the patient came to the office with membranes balging to the introitus. Abortion followed immediately. It was decided that the original cervicoplasty was inadequate, and this was repeated with use of a cufis graft from the thigh. The postoperative cervicohysterosalpingograms showed a satisfactory result with no change in the lumen of the cervical canal before and after irrigation with bromelain.

The next pregnancy (1955) proceeded without event until the seventeenth week. Increasing mucoid discharge that became mucopurulent and then frankly purulent was evident over a period of 5 days. The discharge was odorless and was not blood tinged at any time. Supportive measures were instituted with good response. Labor began spontaneously and after 48 hours of good contractions a fetus and placenta were finally extruded through the cervix that at no time dilated more than 3 cm. There was considerable concern at the time regarding whether the uterus could be evacuated without abdominal interference. After antibiotic therapy, a dilatation and curettage was performed. No cause could be found for the amnionitis from the aborted specimen or the dilatation and curettage. The last cervicoplasty had produced a rigid cervix about 5 cm. long and incapable



Fig. 5. A wedge of one fourth of the cervix is excised from the external os to the level of the internal os.

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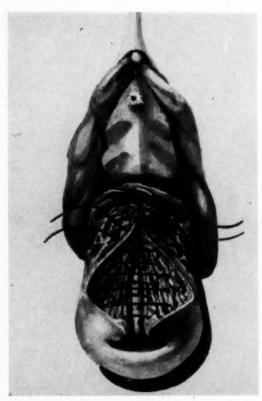


Fig. 6. The three layers of suture.

of effacement and dilatation beyond 3 cm. and that after 48 hours of hard contractions.

In December, 1956, the patient was seen with a twin pregnancy which proceeded very normally until the thirty-sixth week. After about 12 hours of true labor and lack of dilatation of the cervix, a cesarean section was performed with delivery of viable twins weighing 3 pounds, 12 ounces and 3 pounds, 4½ ounces, respectively.

At the time of cesarean section the cervix had not effaced and was 6 cm. long and of uniform caliber 1.5 cm. Contraceptive practices have prevented further pregnancies.

Case 2. Only one other patient has become pregnant and has lost the pregnancy. This 33-year-old woman had had 2 abortions at 20 weeks followed by a breech delivery at 37 weeks of a 5 pound, 12 ounce baby. Four abortions at from 6 to 14 weeks followed this delivery. In 1956 she carried normally until 22 weeks when an incompetent cervix was noted with bulging membranes followed by painless extrusion of the intact amnion.



Fig. 7. The cutis graft applied and sutured in place.

Hysterosalpingograms, performed after the termination of this gestation, showed a structurally incompetent cervical os with superimposed physiologic incompetence. Cervicoplasty with cutis graft was performed. A salpingogram 4 months later showed satisfactory results.

Pregnancy has occurred twice since the operation, each time terminating in abortion at 12 weeks or less. Examination of the curettings following these losses show degeneration of the villus very similar to that described by Gray. The cervix has remained competent.

Case 3. A 36-year-old patient had been pregnant only once with delivery at 24 weeks. Infertility followed. As part of the infertility study salpingograms were done which showed dysfunctional incompetence of the internal os. Cervicoplasty with cutis graft showed satisfactory results when checked by salpingograms. Pregnancy followed with elective cesarean section at 38½ weeks produced a 6 pound, 7½ ounce normal baby. A repeat cesarean section was done about 1½ years later to deliver a 6 pound, 15 ounce infant. At the time of each of these operations

the cervix was checked and was found to be 4 to 5 cm. in length with a lumen of 1.5 cm.

Case 4. The patient was a 34-year-old multipa a whose first pregnancy resulted in a term d livery of a 6 pound infant. She had had mild toxemia. Subsequently she had abortions at 8 weeks and 6 weeks. These were followed by carettement which showed pregnancy tissue. The next two pregnancies carried to 16 and 18 weeks with the typical midtrimester losses due to cervical incompetence. It is of interest that hysterosalpingograms were done in 1952 before we began using bromelain and they were reported normal, showing a competent cervix. In 1954 the x-ray examination was repeated with use of bromelain, and dysfunctional incompetence was found. A cervicoplasty with cutis graft was performed in February, 1956. The patient became pregnant in July, 1956, and carried uneventfully for 38 weeks and was delivered by cesarean section. At operation the cervix was found to be competent. Contraceptive practices have prevented further pregnancies. Of some interest is the fact that during this pregnancy the patient was infected with trichinosis. A rather stormy course accompanied the infection, and at one point the diaphragm was involved. It was felt that the uterus might have been involved because of extreme tenderness and some irritability. Sections of the myometrium submitted for examination at the time of cesarean section failed to show any evidence of infestation although biopsies of other muscles had been positive.

Case 5. The patient, a physician's wife, was a 23-year-old multipara whose first delivery occurred at term. Six subsequent pregnancies resulted in abortion, one at 22 weeks, two at 20 weeks, one at 19 weeks, and the remaining two at 15 to 17 weeks. Salpingograms showed a normal cervical canal on the primary films and a dramatic change after irrigation with bromelain. Cervicoplasty with cutis graft rendered good results when rechecked by x-ray. At this point the patient went to Europe to join her husband who was stationed there. Pregnancy ensued and she carried uneventfully to labor at term. In spite of suggestions that she undergo carean section she was allowed to deliver viginally. A postpartum hemorrhage from a Crvical laceration occurred. The lost blood was placed, the laceration was repaired, and the patient made an uneventful recovery. Subsequently, she has been delivered of 3 more infants at term with no difficulty. This case demonstrates the fact that vaginal delivery is possible in these cases, but we would choose to resort to cesarean section.

Case 6. A 20-year-old multiparous housewife was first delivered by cesarean section for cephalopelvic disproportion and breech presentation in 1953. A repeat section was performed in 1955 at 39 weeks, resulting in the birth of an infant weighing 5 pounds, 5 ounces. In April, 1957, she had an abortion with demonstrated incompetence of the cervix at 27 weeks. She promptly became pregnant again and had a repeat abortion at 27 weeks in December, 1957. April, 1958, cervicohysterosalpingograms demonstrated an anatomically incompetent internal os with superimposed dysfunctional incompetence. A satisfactory result was obtained by cervicoplasty and cutis graft. Pregnancy followed and proceeded uneventfully for 38 weeks, when the patient was delivered by cesarean section.

Case 7. The patient was a 22-year-old multipara who had been delivered of one infant at 39 weeks. There followed 3 pregnancies with spontaneous painless premature deliveries at 18, 20, and 21 weeks. Cervicohysterosalpingograms showed mild anatomic and severe dysfunctional incompetence. A cervicoplasty and cutis graft were performed and checked by repeat hysterograms which showed satisfactory correction. Pregnancy occurred and was carried to 381/2 weeks when she underwent cesarean section.

Comment

The physiologic or dysfunctional type of cervical incompetence seems to be a unique entity. Its demonstration by x-ray techniques is easy and has proved consistently correct as demonstrated by the failure of patients in the nonoperated group to carry to term. The Lash repair is inadequate in patients with this type of incompetence as demonstrated in 3 patients, 2 of whom had abortions after the Lash repair. The adequacy of the cutis graft is demonstrated by the cases in which the patients became pregnant after the grafting and continued to term with the exception of the two losses cited. This was particularly well demonstrated in Case 1.

The operation has in no way interfered

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with fertility. It is true that patients with physiologic or dysfunctional incompetence as well as with the other types of incompetence may be carried to term by a pursestring suture of the cervix in pregnancy when dilatation occurs with bulging of the membranes. The success rate varies, however, from 60 per cent in the original work of Shirodkar¹ to 80 per cent in the recent paper of Taylor. There will always be cases where it is too late to salvage the pregnancy by the purse-string or tourniquet method. It does seem more logical to prevent this occurrence rather than chance even the 80 per cent success of suturing.

Summary

A method of diagnosis and repair of physiologic or dysfunctional incompetence of the internal os has been presented.

A review of films of 147 patients showed incompetence of this type in 24 patients. Fifteen patients refused operation, and, of these, 5 have become pregnant only to have spontaneous abortions as before, i.e., after 12 weeks. Surgical correction by means of a cutis graft has been used in 9 patients. Pregnancy has occurred in 7. Six patients have been delivered of 11 living infants at or near term. Seven case histories are included.

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Review of 36 Shirodkar operations

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RECOGNITION of the incompetent cervix and its role in fetal wastage has been well documented in the past decade.^{4, 6} The purpose of this paper is to review the problem as recognized and managed in the Maternity Divisions of the Buffalo General and the Buffalo Children's Hospitals, two closely related services delivering approximately 5,000 patients annually. This study is based on the records of 35 women in whom the clinically incompetent cervices with but one exception were treated surgically while the patient was pregnant within the past 27 months.

The diagnosis was based, as is now generally recommended, upon one or both of the following criteria: (1) history that the spontaneous onset of labor in the middle trimester of pregnancy was preceded by premature rupture of the membranes; (2) visualization and/or palpation of the cervix during the second trimester indicated effacement and partial dilatation of the cervix with protrusion of membranes. A third factor but considered only confirmatory was a history suggesting trauma to the cervix, difficult delivery with the probability of cervical laceration, or repeated dilatation and curettages.

Table I indicates the number of patients showing one or more of these criteria.

All operative procedures were performed by the obstetrician-gynecologists of the attending and resident staffs of the two hospitals. Eleven different operators performed the 36 procedures reviewed. The typical patient was approximately 30 years of age, with an average of 5.2 previous pregnancies that had resulted in the survival of only 1.1 infants per patient. Previous premature labors had usually occurred at the twenty-second week of gestation. In the current pregnancy the average gestational age of the fetus was 17.1 weeks at the time of the operative procedure. One patient had the procedure performed in two consecutive pregnancies without successful outcome.

The surgical technique was essentially that outlined by Shirodkar⁵ with the exception of the suture material, which varied considerably as indicated in Table II.

In 6 instances at the onset of premature labor the suture material was found to have either pulled out or sloughed off from the cervix despite the use of anchoring sutures. With umbilical tape, nylon mesh, and Dacron mesh this accident occurred twice with each material. In one instance the reverse was true and an attempt was made to remove the Dacron mesh from the patient in active premature labor with evident premature separation of the placenta. In this instance the mesh was so thoroughly embedded that its excision was impossible, and an emergency hysterotomy was employed. Blood loss was not a usual problem although 2 patients each required 2 units of blood during and after operation. In both of these instances the bleeding occurred in the area of the bladder reflection. There were no operative and no maternal deaths in the series.

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Table I

	No. patients
A. History of spontaneous onset of	f labor
in second trimester	
Preceded by rupture of the	
membranes	18
 Findings on examination in currer pregnancy 	nt
Cervix partially dilated and/o	or
effaced	14
Membranes protruding	10
C. Patients who had both A and B	11
D. History of spontaneous onset of l	abor
in second trimester following	
Complicated vaginal delivery a	at
term	4
Uncomplicated vaginal deliver	-
term	10
Dilatation and curettage of the	
uterus	8
uterus	0

Table II

Silk	15
Nylon mesh	9
Dacron mesh	4
Umbilical tape	4
Fascia lata	1
Monofilament nylon	1
Wire in polyethylene tubing	2

Table III. Analysis of failures—present pregnancy

Bleeding and pain followed by	
premature labor	9
Premature rupture of membranes	
followed by premature labor	1
Placenta previa	1
Operative failures (within 48 hours)	2

Table IV. Analysis of failures—previous pregnancies

History of two or more first	
trimester abortions	5
Bleeding and pain with second	
trimester abortion	6
Premature rupture of membranes	
followed by premature labor	1

Results

There were 16 live births without hysterot omy or cesarean section, of which number 6 babies weighed less than 2,500 gram Four of these labors were electively induced at term with intravenous Pitocin and amniotomy. In all instances of vaginal delivery the suture material was excised in the delivery room early in labor without anesthesia. In most instances at delivery it was evident that the suture material had been only incompletely removed, due to its adherence to the cervical stroma. Three patients developed bilateral cervical lacerations that were repaired after delivery. Eight patients were delivered by cesarean section, resulting in 7 live births. The loss of one stillborn infant by cesarean section was due to premature separation of the placenta and inability to quickly remove the mesh which had been used to close the cervix.

Comment

With increasing experience the obstetrician-gynecologist will employ this operation with a lower morbidity, eliminating excessive bleeding, inadvertent rupture of the membranes, and the inclusion of improperly selected cases. Failure in this series seemed associated with bleeding, development of pain, and subsequently premature labor. This is illustrated in Table III.

Of importance are common factors in the obstetrical histories of these 12 patients that would enable us to select proper patients for this operation. Table IV records these factors.

One patient in whom bleeding and abortion occurred after suturing was found postoperatively to have a bicornuate uterus.

Among the 23 patients in whom the procedure was successful, only 3 had a history of two or more first trimester abortion. Three patients had evidence of premature separation of the placenta and second trimester abortion.

Vaginal delivery involves the risk of cetain inherent difficulties, particularly the inability to free the cervical suture sufficienty to permit full dilatation and unobstructed , 1961

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delivery. Severe cervical lacerations were sestained in 3 patients despite apparent excision of the constricting band of suture material. However, we believe vaginal delivery should be considered for the small premature infant, whose chance of survival after vaginal delivery may be greater than can be expected following delivery by cesarean section. It remains to be seen if the cervix, once negotiated, will retain a dependable degree of competence or require repeated operation in a subsequent pregnancy.

Summary

In 169 previous pregnancies this group of 35 mothers had produced but 26 surviving children for a fetal salvage of only 15.3 per cent. Only one patient had produced a live child as a result of her last pregnancy, i.e., the one immediately preceding the pregnancy in which the Shirodkar procedure was done. After suture-closure of the cervix, among 36 pregnant patients, 23 of the pregnancies re-

sulted in the birth of a surviving child, a fetal salvage of 63.9 per cent.

It appears that patients who have a history of repeated first trimester abortion or a history of premature separation of the placenta and second trimester abortion are not likely to be successful candidates for this operation.

This operation is indicated when effacement, beginning dilatation, and visualization of membranes occur in the absence of bleeding and pain, in the second trimester.

This operation seems indicated when, in a previous pregnancy, second trimester spontaneous rupture of the membranes has occurred without bleeding and pain.

The relative simplicity and apparent safety of this procedure suggests its use in any intelligently managed obstetrical practice. Better results will be realized when there has been a more careful selection of cases by obstetrician-gynecologists experienced in the technique of this procedure and in the management of these patients.

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Simple treatment of the incompetent cervical os

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IF, AT ALL, the "bag of waters" acts as a hydraulic wedge,1 it is no more strikingly demonstrated than in its effect on the incompetent cervical os. This is not engendered by labor but simply by the growth of the ovum within the confines of the uterus. Under this steady and mounting pressure the components of the internal os and the inferior segment give way. Whether or not this inadequacy is traumatic2 or congenital, the pattern is essentially the same. The membranes eventually sacculate into the weakness and rupture. In time labor is initiated and the contents of the uterus are expelled. The condition is repetitious. Various operations have been devised for its correction-all of which seem to be directed toward the accentuation of resistance to this hydrostatic force-the operations of Lash and Lash,3 and Shirodkar4 being the more notable. If, however, nothing is done, the cervix, with its axis directly and centrally aligned with the relatively nonresistant vagina, lends itself to its own dissolution (Fig. 1). Logically then, any device which can alter this collineation so that the force is directed toward firmer bearings would do much to discourage this tragic waste. The Hodge or Smith pessary may have some merit in just such therapy-first, by changing the inclination of the cervical canal, later, by distributing the weight of the now growing ovum through the lower uterine segment onto the cul-de-sac, the vaginal floor, and the retrosymphyseal osteomuscular structures (Fig. 2). In addition, the tension exerted on the uterosacral ligaments will have a "sling" effect on the anterior cervix through their splayed continuity with the cervical fascia (Fig. 2, inset), thus compressing the cervical canal—at least for the earlier part of the pregnancy.

Interesting are the following cases:

Case 1. Mrs. S., a 29-year-old patient, presented herself for examination in February, 1954. She had miscarried twice, once at 4 months and again at 5 months; each miscarriage was preceded by spontaneous rupture of the membranes. Her immediate complaints led to the findings of acute pyelitis and chronic cervicitis; both conditions responded to appropriate treatment. The uterus was retroverted. In October, because she had not been able to conceive again, a Smith pessary was inserted with gratifying prompt results-her last menstrual period occurred on October 25. Because of the history of premature rupture of the membranes and perhaps because the Shirodkar procedure had not yet gained prominence, the pessary was allowed to remain and the patient returned to the office for frequent cervical observations. There was no sacculation and at 71/2 months the instrument was removed. Delivery occurred August 3, 2 days after the expected date of confinement. The duration of labor was one hour and the infant weighed 7 pounds, 11/2 ounces.

In November, 1956, the patient returned, again pregnant; her last menstrual flow had occurred on October 9. Again a pessary was inserted because of the previous success. However, on February 20, at approximately 4 months' gestation, sacculation of the membranes was noted. The patient was hospitalized for a cervical os operation. At the very beginning of the procedure, unfortunately, the membranes ruptured, and the expulsion of the uterine contents followed shortly. It was noted during this

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Howely 4 praces for a ing of braces e conag this time that the pessary which had been inserted was unusually small for the purpose for which it was intended although when it was first interted it had been snug and tight. Had the changes in the vagina under the influence of pregnancy necessitated a larger pessary?

An opportunity to answer this question presented itself when the patient again returned for obstetrical care in October, 1957. The last menstrual period had occurred August 21 and the due date was estimated to be May 28. A snug pessary was inserted which after one month was found to be lacking in support. A larger one was then substituted and carefully observed at frequent intervals. It sufficed until April 25 when it was removed. Delivery was uncomplicated on the expected date of confinement. Labor lasted 4 hours and 40 minutes; the infant weighed 7 pounds, 8½ ounces.

Case 2. Mrs. G., a 29-year-old patient, presented herself for obstetrical care in February,

1959. She had had 4 miscarriages at 3, 4, 4½, and 2 months, respectively, and 2 premature deliveries at 6½ and 6 months, respectively, neither baby lived. Three of these episodes were known to have been preceded by sacculation and spontaneous rupture of the membranes.

The estimated date of confinement was September 19; the last menstrual period had occurred on December 12. A Smith pessary was inserted, and the patient was carefully followed. The pessary appeared adequate until June 22 when a larger one was substituted. The patient continued to wear the pessary until September 8 when it was no longer deemed necessary. Uncomplicated delivery occurred on September 10; the infant weighed 7 pounds, $6\frac{1}{2}$ ounces.

Case 3. Mrs. G., a 23-year-old patient, presented herself for obstetrical care in April, 1959. The expected date of confinement was estimated to be Oct. 14, 1959. Two previous pregnancies had terminated in late abortions (both at 6½

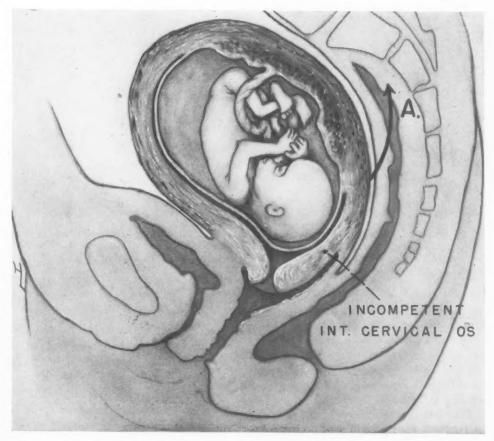


Fig. 1. Axis of damaged cervical canal in alignment with that of the relatively nonresistant vagina. A indicates the direction of the uterosacral ligamentous support.

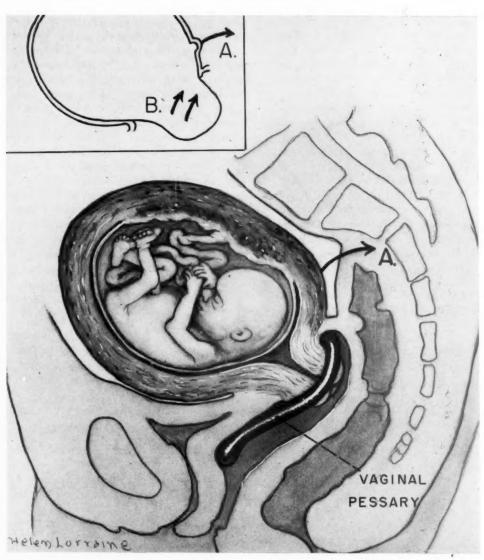


Fig. 2. With the aid of the pessary, the cervical axis is directed toward reinforcement. A indicates the altered direction of the uterosacral ligaments. Inset. A indicates the altered direction of the uterosacral ligaments; B indicates the direction of the "sling" support to the cervix

months), the last despite the fact that a Shirodkar procedure had been done at 22 weeks because of cervical dilation and protrusion of the membranes.

A Smith pessary was inserted on the patient's first visit and was replaced with a larger one on July 16. On September 29 the patient went into labor spontaneously. The pessary, at this time, was removed. After an 8 hour, 52 minute labor the patient was delivered of a 7 pound, 8 ounce infant.

Conclusions

A simple treatment for the incompetent cervical os has been suggested. Out of 5 pregnancies, there were only 4 living infants, and these four live births apparently we effected by the procedure outlined. While these results are impressive, more patients will have to be thus treated to warrant any conclusions.

In all of these cases the cervix seem d

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to efface considerably in the last trimester, indicating a loss of the internal os, but the

external os remained "closed" until that time when dilation would normally be expected.

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Atypical changes of genital epithelium associated with ectopic pregnancy

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PREGNANCY in the human female is accompanied by numerous rather momentous changes. Naturally, the most profound alterations take place within the reproductive system, and the uterus in particular. Many of these alterations have been clearly defined, others undoubtedly await discovery. Since the publication of the illuminating paper by Arias-Stella¹ in 1954, considerable interest has been turned toward the atypical changes which occur in endometrial epithelium when there is trophoblastic tissue present within the body. These changes consist of focal enlargement of the gland cells with nuclear hypertrophy and hyperchromatism. There is a piling up of gland cells resulting in intraluminal tufts and a loss of cell boundaries. Vacuoles are formed within these tufts and there is a loss of cellular polarity. There is considerable variation in the size of the nuclei, some achieving 4 times the normal size. Mitoses are also seen in these atypical areas. The quantity of cytoplasm is likewise increased and, in addition to the presence of vacuoles, the appearance of the cytoplasm is foamy. Because of this glandular hypertrophy the lumina of the glands are diminished and, at times, obliterated.

These alterations were present in the endometrium in 20 of 182 cases of abortion: in 16 of 26 cases of hydatidiform mole; in 3 of 14 cases of choriocarcinoma and chorioadenoma; in 2 of 4 cases of syncytial endometritis and in 1 patient with ectopic pregnancy reported by Arias-Stella.1 This reaction of the endometrium was seen in the upper two-thirds of the glands and the basilar portions were not involved. It was most commonly accompanied by decidual reaction but was also seen where no evidence of decidua could be found. It was usually related to secretory or mixed endometrium presenting some evidence of proliferative activity. Arias-Stella believed these atypical alterations of the endometrium were due to the "unique overstimulation" from increased estrogens and progesterone occasioned by the presence of chorionic tissue. The following year (1955) he reported² successful production of these changes by giving chorionic gonadotropic hormone plus estrogen to animals with intact gonads. This same transformation was accomplished by giving estrogen plus progesterone to castrated rats over the same period of time (18 to 20 days). By using estrogen alone, he was unable to obtain the same effect in both castrated animals and those with intact glands.

Ferguson³ mentioned the enlarged, irregular, and hyperchromatic nuclei in 194) and pointed out their ability to create mininterpretation of cytosmears following about

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tions. Hilrich and Hipke4 have more recently made the same observation. These atypical changes were previously described by Deelman⁵ in 1933 who believed that they could be confused with malignant transformation. He felt that they represented degenerative changes and alterations due to the inflammation so frequently seen in abortion. de Brux and Vaissade,6 in studying this cellular atypism, have come to the same conclusion. Most investigators of this problem seem to agree with Arias-Stella that these changes are probably hormonally induced. These atypical changes in association with ectopic pregnancy can be so marked that they actually suggest endometrial malignancy. In 1956, Truemner of Rockford, Illinois, reported the case of a 40-year-old woman with an unsuspected ectopic pregnancy whose endometrium, obtained by curettage, displayed "malignant alterations." Upon operation, an unruptured tubal pregnancy was discovered. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed and, in retrospect, these changes of the endometrium were believed to represent those described by Arias-Stella. Most authors⁸⁻¹⁴ have pointed out that although these atypical cellular changes may mimic malignant transformation, it is clearly a benign process. This has been shown to be true by Roach, Guderian, and Brewer⁸ who made a most comprehensive study of the Arias-Stella reaction. They were unable to demonstrate these changes in association with any of 100 specimens of adenocarcinoma of the endometrium studied.

Pildes and Wheeler9 in 1957 reported the presence of this atypical reaction in 13 of 50 endometria obtained by curettage from patients with ectopic pregnancy. Since 4 of their cases with atypical change had no decidua, they concluded that the presence of these alterations without trophoblastic villi in curettings should increase one's suspicion ol ectopic pregnancy. In a prospective study of curettage specimens, Frederiksen¹⁰ has found these changes to be of considerable value in suggesting the diagnosis of ectopic piegnancy, provided recent intrauterine

pregnancy could be excluded. Others^{6, 11, 18} have made the same observation by considering minor degrees of alterations. Berthelsen11 in 1957, in reporting a case of atypical endometrial reaction associated with ectopic pregnancy, sagely suggests that this atypical change is only of value when present. Its absence should not be misinterpreted to mean that there is no ectopic pregnancy, just as absence of decidual tissue should not be similarly misconstrued.

These changes have been shown to be present in intrauterine pregnancy. Möller¹² reported the Arias-Stella reaction in the opposite horn with pregnancy in one horn of a bicornuate uterus. Arias-Stella¹³ reported 3 instances of "minimum atypia" in apparently normal early intrauterine pregnancy. We have observed these changes in material from therapeutic abortion. Roach, Guderian, and Brewer⁸ have reported a higher incidence in term pregnancy than with choriocarcinoma, syncytial endometritis, or hydatid mole. It is quite evident, therefore, that if these alterations are to be used as an aid in the diagnosis of ectopic pregnancy, intrauterine pregnancy must be excluded.

That the endometrium may be displaced from the uterine cavity, as in endometriosis, and yet share in this atypical reaction is also known. Tweeddale and Hoffman¹⁴ reported a case wherein atypical change was found in an endometriotic nodule associated with tubal pregnancy. Möller12 has more recently presented 2 instances of the Arias-Stella reaction in endometriotic lesions in association with early intrauterine pregnancy that were apparently proceeding normally. The purpose of this paper is to further elucidate factors influencing these endometrial changes, and to report similar changes taking place in the tubal epithelium as well as in adenomyosis associated with ectopic pregnancy.

Material and method

This report is based upon the histologic study of the genital tissues obtained from 144 patients with proved ectopic pregnancy.

Table I. Types of endometrium

	Pat	ients		No. with atypical		
Type	No.	%	No. with decidua	change		
Secretory	89	62	50	72		
Proliferative	29	20	0	0		
Mixed	22	15	3	15		
Resting	4	3	0	0		
Total	144	100	53 (37%)	87 (60%		

They were managed on the Tulane Service at Charity Hospital in New Orleans from Jan. 1, 1952, through Dec. 31, 1958. All of these patients were treated by total hysterectomy plus unilateral or bilateral salpingectomy or salpingo-oophorectomy. The majority of these patients received abdominal total hysterectomy and unilateral salpingo-oophorectomy. Over this 7 year period a much larger number of patients with ectopic pregnancy were managed by the Tulane Service. In fact, in only about 1 out of 4 seen with ectopic pregnancy was hysterectomy found to be necessary and advisable. The indications and rationale as well as the results of this form of therapy are beyond the scope of this paper and are presented in a previous communication by Beacham, Webster, and Beacham.¹⁵ In all 144 cases, 1 or more uterine blocks were available for evaluation of the endometrium and myometrium. No endometrium obtained by curettage was used for this study. Originally some material so obtained was included but it soon became apparent that endometrial tissue from uterine blocks was somewhat superior for this investigation.

The oviducts were studied in 116 instances. One hundred and two ovaries, including 47 corpora lutea of pregnancy, were available for histologic study. This permitted evaluation of the endometrium and correlation with the duration of uterine bleeding and extent of degeneration of villi with the degree of regression of the corpora lutea. The tissues were fixed in 10 per cent formalin. Sections 5 to 7 microns in thickness were made and stained with hematoxylin and eosin.

Age and race

The age of these patients ranged from 19 to 42 with an average age of 32. This is somewhat older than the average age for all patients seen with ectopic pregnancy at Charity Hospital. There were 14 white patients and the remaining 130 were Negroes. The white patients fell into an older age range with an average age of 35 years.

Endometrial findings

The type of endometrium present was evaluated and, as shown in Table I, was found to be secretory in 89 instances, or 62 per cent of the entire series. Decidualized stroma was present in 50 of the 89 and there were 72 in which the atypical change could be found. The decidual change was usually confined to the upper half of the thickened endometrium and the included glands were lined by flattened atrophic cells. The deeper portions of the glands, where decidua was lacking, were usually quite hyperplastic and commonly displayed the atypical changes as previously described (Figs. 1 and 2). The basilar portions of the glands failed to enter into this transformation but often demonstrated some degree of secretory response. Proliferative endometrium was encountered 29 times and there were none with decidua or atypical epithelium. Mixed secretory and proliferative endometrium was demonstrated in 22 patients of whom 3 had decidua and 15 the atypical reaction. The mixed type endometrium displayed definite secretory glands but often the stroma was proliferative. In some, there was a curious mixture of secretory gland cells in the surface por-

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tons of the glands with active proliferations going on in those of the deeper regions. The surface portions of 3 of these contained remnants of mature decidualized stroma. It appeared as though the endometrium had desquamated but not completely, following which proliferative activity had begun. The endometrium was of the resting type in 4 instances and represented nearly complete desquamation without any subsequent stimulation to proliferate. Only the basal portions of the glands remained and they were lined by inactive low columnar to cuboidal cells. None of these demonstrated the atypical change.

From the totals in Table I we see that decidual reaction was present in 53 (37 per cent) of 144 endometria associated with ectopic pregnancy and was limited to those of secretory or mixed types. The atypical epithelial reaction was observed, at least to some degree in 87 (60 per cent) of the 144 cases studied and was likewise limited to the secretory or mixed types. In 43 of these, or 30 per cent of the 144 cases, the changes were minimal and in only 9 cases, or 6 per cent, were the changes considered marked. Inflammation was associated with only 12 (14 per cent) of the 87 endometria with atypical endometrial reaction so it does not appear to be the cause, as some3, 5, 6 have inferred. Age also was not found to be a factor in the production of these atypical changes. There was, however, significant difference in the duration of uterine bleeding in the patients whose endometria fell into the various categories (Table II). Those with decidualized or secretory endometrium had been bleeding for shorter periods of time than the average for the entire group. Tose with mixed, resting, or proliferative types of endometrium had been bleeding for average durations greater than that of the en ire group, which was 14.4 days. Of course, there were individual variations—for in tance: several patients with mixed endometrium had been bleeding less than 14 days but the flow had been fairly heavy. There were some with decidua who had been bleeding 20 or more days. The bleeding in

these instances was slight spotting. The patients with atypical endometrial reaction were bleeding for an average of 11.5 days, whereas the average for those without it was 19 days. This suggests that more of the patients had this atypical secretory hyperplasia at an earlier date and that the endometrium containing these focal atypicalities had been desquamated and passed. The atypical reaction was not seen where significant bleeding had been present for 30 or more days. A study of the interval from the last normal menstrual period to the day of operation was also revealing. There were no atypical reactions in the 9 patients who were operated on less than 32 days after the last menstruation. In those operated on with greater interval, this finding was not uncommon. So it would appear that about 33 days are required for the atypical endometrial reaction to develop in association with ectopic pregnancy. There were 13 patients with no interval bleeding and those intervals from the last menstrual period to operation were greater than 35 days. Three of these failed to demonstrate any atypical alterations or presence of decidua. Since the endometria of these 3 were entirely intact, we must conclude that not all endometria in ectopic pregnancy develop the atypical reaction or decidua.

Findings in displaced endometrium

17 Endometriosis was encountered in patients. Internal endometriosis

Table II. Endometrial categories and duration of bleeding

Type of endometrium	No. of patients	Average duration of bleeding (days)
Decidualized	53	9.8
Secretory	89	10.2
Mixed	22	22
Resting	4	24
Proliferative	29	24.5
With atypical reaction	87	11.5
Without atypical reaction	57	19
The entire group	144	14.4

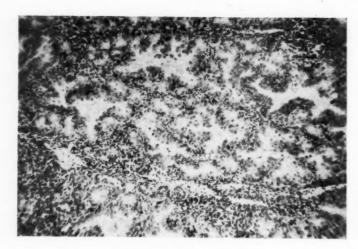


Fig. 1. The endometrium of a patient with ectopic pregnancy. The atypical epithelial changes as described by Arias-Stella are present (low power).

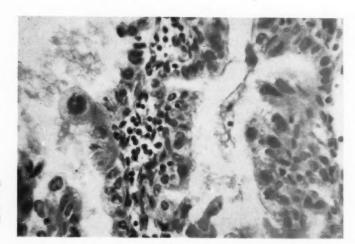


Fig. 2. This high power view is from the same uterus as shown in Fig. 1 and comes from the central portion of the endometrium. The atypical reaction is clearly evident.

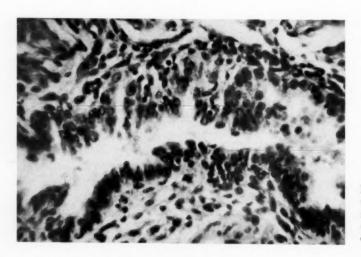


Fig. 3. Adenomyosis associated w th tubal pregnancy showing the atypical reaction. The endometrium in his case displayed decidua and the same epithelial changes (high power)

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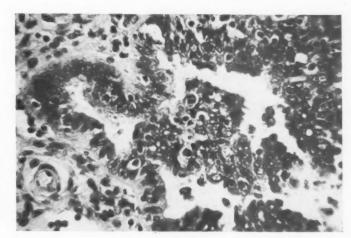


Fig. 4. Fallopian tube under high power with atypical appearance of epithelium. The perinuclear vacuolization is shown and a moderate amount of anaplasia is evident.

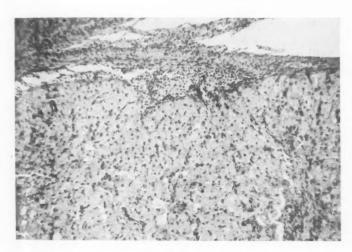


Fig. 5. Corpus luteum of pregnancy with mild degree of regression. The endometrium in this instance revealed the atypical alterations and decidua (low power).

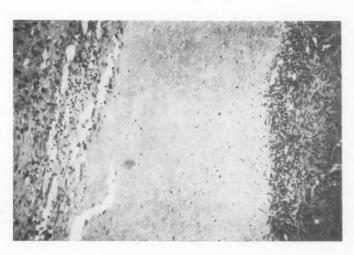


Fig. 6. A corpus luteum of pregnancy with marked regression. The associated fetal villi were markedly degenerated and the endometrium was proliferative (low power).

w th ypi al is same er) served in 13 of the 144 uteri studied, an incidence of 9 per cent. Only those cases were included wherein the adenomyotic lesions penetrated deeper than 5 mm. below the basilar portions of the endometrial glands. External endometriosis was found in 4 of the 104 ovaries that were studied histologically, an incidence of 3.9 per cent. Endometriosis was rare in this group of patients, just as fibroids and chronic salpingooophoritis were rather common. The atypical endometrial reaction, as shown in Fig. 3, was found in the lesions of 3 of the 13 adenomyotic uteri. The endometrium lining the cavity of these 3 uteri also contained the atypical alterations. In 7 uteri atypical endometrium was present, lining the cavity, but the adenomyotic lesions failed to demonstrate response to hormones. In 3 instances both the endometrium and the adenomyosis were in phase with each other but neither demonstrated the atypical alterations or decidua. The atypical epithelial changes were present in 2 of the 4 instances of ovarian endometriosis.

As shown in Table III, we found a total of 17 cases of endometriosis of which 5 (29 per cent) had the atypical transformation. This incidence is only one half that found in the endometrium associated with ectopic pregnancy. We might expect this since in one half of the endometriosis cases, the lesions were out of phase with the endometrium of the uterine cavity and failed to demonstrate response to the increased hormones. Decidual reaction was present in the lesions of 2 of the 17 endometriosis cases and again was less frequently found than in the endometrium associated with ectopic pregnancy.

Table III. Findings in endometriosis

Lesion	No. of patients	Atypical reaction	Decidua	
Adenomyosis	13	3	1	
Ovarian endometriosis	4	2	1	
Total	17	5 (29%)	2	

Tubal findings

The Fallopian tubes were available for study of multiple sections in 116 of the 144 cases of ectopic pregnancy. The mucosa and tubal wall as well as the villi were evaluated. Definite decidual reaction was present in 20 of these 116 tubes, an incidence of 17 per cent. There were 50 others in which decidua-like reaction could be found but it was not at all comparable to that of the endometrium. Nineteen of the 116 tubes contained what we believe to be an atypical hypertrophic reaction, not unlike that described for the endometrium. This is an incidence of 16 per cent as compared to the 59 per cent found in the endometria of these 116 patients. This reduced incidence of tubal atypia may be due to the fact that the tubal epithelium is less responsive to hormones.

There is focal epithelial hyperplasia with cells piled up into the formation of buds projecting into the lumen which lends a ragged, scalloped appearance to the surface. Within these projecting buds the cells are enlarged, having lost their polarity as well as the cellular membranes. There is an increase in nuclear size, variation in size, shape, and hyperchromatism. Mitosis is not uncommon and many nuclei display chromatin clumping. Vacuoles are often seen surrounding the nuclei. The cytoplasm is neither pale staining nor foamy as in the atypical endometrial reaction but the architectural and nuclear alterations are just as profound (Fig. 4). Decidua was present in 15 of the 19 tubes with atypical epithelial hyperplasia, while advanced degree of inflammation was found in only 7. So it appears that increased hormone stimulation produces these changes rather than degeneration. As previously mentioned, the residual of antecedent infection with formation of multiple adhesions, hydrosalpinx, distortion of tubal rugae, and interrugal adhesions were rather common. Tuberculous salpingitis was present in 1 patient but the endometrium studied in this case failed to demonstrate any evidence of tuberculosis. The tubal mucosa was quite abnormal in appearance having assumed a

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seudoglandular pattern with somewhat reperactive epithelium. This, however, differed from the atypical reaction, in that there vere no tufts or increase in mitosis. Also the focal nuclear alterations were not present in the tuberculous tube.

An evaluation of the chorionic villi revealed all gradations of degeneration. We have classified these into 4 categories as shown in Table IV. The findings in the endometria of each group were then tabulated so that correlation of the degree of villus degeneration with the presence of the atypical reaction and decidua is presented. Fifteen without significant degeneration were accompanied by 13 endometria with atypical reaction and 11 showing decidual change. The occurrence of the atypical endometrial reaction and decidua both diminished with advancing degrees of villus degeneration. It was also noted that as the degree of villus degeneration increased the average duration of bleeding for the group increased.

Ovarian findings

The ovaries were available for study in 102 of the 144 cases herein presented. Ovarian endometriosis was found in 4 of these, with the atypical reaction in 2. The evidence of antecedent infection was frequently seen. There were numerous adhesions and often fixation of the tube to the ovary, with fibrosis. Two old tuboovarian abscesses were present, with calcium deposits in the wall of 1. Bilateral benign cystic teratomas were found in 1 patient. The inflammatory response to chemical irritation from the degenerating blood was also frequently seen. Marked luteinization of the thecal cells about the larger follicles was a common finding. Occasionally Juteinization of the stromal cells not near any follicles could be seen.

Corpora lutea of pregnancy were available and studied in 47 cases. The size usually ranged from 2 to 3½ cm. in greatest diametcr. Two were larger, 6 and 7 cm. in diameter, and cystic. When regression of the co pus luteum was present it was more evide t in the granulosa portion. All degrees

Table IV. Correlation of degree of villus degeneration and endometrial findings

Villus degenera-	No. of	With atypical endome- trial reaction		With decidua		
tion	patients	No.	%	No.	%	
None	15	13	87	11	73	
Mild	29	25	86	17	59	
Moderate	34	17	50	12	35	
Marked	38	14	37	4	10	
Total	116	69	59	44	38	

of regression were exhibited in these 47 corpora lutea (Fig. 5). As regression increased, there was diminishing vascularity, pyknosis of the nuclei, or karyoklasis, pallor of the cytoplasm, and finally disruption of the cell membrane. As this continued, the structure became hyalinized and fibrotic with notable reduction in size (Fig. 6). The 47 corpora lutea were classified into 4 categories or degrees of regression and these were correlated with the endometrial findings and with the average duration of uterine bleeding (Table V). In the 15 instances were regression was minimal, the associated endometria of 14 revealed the atypical reaction. Decidua was present in 12 of these whose average duration of bleeding was 6.5 days. As regression of the corpus luteum advanced, the average duration of bleeding increased and the incidence of associated atypical endometrium and decidua progressively decreased (Table V).

It is apparent then that, as the corpus luteum undergoes regression and the estrogenic and progestational support of the endometrium diminishes, there is progressive desquamation with successive loss of decidua and the portion of the endometrium containing the atypical reaction. That this desquamation proceeds according to the basic pattern present in normal menstruation was established by Jones and Brewer.¹⁶ The process is usually somewhat protracted and in 22 per cent of our cases apparently incomplete, resulting in mixed endometrium.

Table V. Corpus luteum regression and endometrial findings

Degree of regression	No. of patients	No. with atypical reaction	No. with decidua	Average duration bleeding (days
Minimal	15	14	12	6.5
Mild ·	15	12	7	12
Moderate	14	5	3	23
Marked	3	1	1	39
Total	47	32 (68%)	23 (49%	6)

Comment

The type of endometrium found in association with ectopic pregnancy has long been of interest. Romney, Hertig, and Reid17 reported decidua present in 19 per cent of 115 cases of ectopic pregnancy where endometrium was available for study. They also gave the aggregate totals of 6 previous reports of 39.6 per cent with decidua in 217 such cases. We have found decidua in 37 per cent of 144 endometria in uterine blocks from patients with ectopic pregnancy. This is comparable to the aggregate totals above. The reported incidence of atypical endometrial transformation with ectopic pregnancy has been quite variable (Table VI). Svensson¹⁸ reported these changes in 3 of 30 ectopic pregnancies with 5 additional specimens showing uncertain changes. Frederiksen¹⁹ reported the Arias-Stella reaction in 41 per cent of 32 cases in a retrospective study. In a later communication¹⁰ he recorded its presence in all of 12 cases of ectopic pregnancy by prospective study of the curettage specimen. Roach, Guderian, and Brewer⁸ recently reported only 1 instance of atypical change in 35 specimens of ectopic pregnancy. They have excluded the hypertrophic adenomatous pattern and minor cellular atypism that we and others6, 9, 13, 19 have apparently included. Arias-Stella¹³ reported 22 positive for these changes in 44 proved cases of ectopic pregnancy, but we are not told whether these were uterine blocks or curettage specimens. I suspect they were largely from curettage or biopsy.

We have found an atypical epithelial reaction of the endometrium in 87 (60 per cent) of 144 patients with ectopic pregnancy. In 43 of these the changes were

minimal, and in only 9 were they considered marked. We feel that the discrepancy of reported incidence can be understood when we realize that there are all gradations from markedly atypical changes to those of very mild degree. Some authors^{8, 18} may have excluded the minor changes. We believe that the in situ endometrium on sections of uterine specimens is superior to that from curettage to demonstrate the atypical changes. We had more than 1 uterine block in only a few of our cases, but additional sections were obtained from the single block in the majority of the cases.

In a recent study of 9 uteri from patients with choriocarcinoma or hydatid mole, Arias-Stella²⁰ has shown the atypical change to be present in all but 1. This was accomplished by serial blocks from the entire uterus. We might have found more atypicalities with more blocks and more sections. We also feel that the patients who have been bleeding for a long time are less likely to have endometrium containing the atypical changes.

Table VI. Reported incidence of A-S reaction with ectopic pregnancy

	Year	No. of	With atypical reaction		
Author		patients	No.	0/1	
Svensson ¹⁸	1957	30	3	10	
Pildes and Wheeler9	1957	50	13	26	
Frederiksen ¹⁹	1958	32	13	41	
Arias-Stella ¹³	1959	44 .	22	50	
Roach, Guderian,					
and Brewer ⁸	1960	35	1	2.9	
Total		191	52	27	

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Factors that influence the presence or absence of the atypical reaction are principally hormonal. In ectopic pregnancy, as the disruption of villi and villus degeneration occur there is reduction in the chorionic gonadatrophic hormone. Consequently the corpus luteum of pregnancy regresses with reduction of the estrogen and progesterone levels thus permitting progressive desquamation of the endometrium. As bleeding continues, there is successive loss of decidua and of the endometrium containing the atypical reaction.

Not all endometria develop decidua or the atypical reaction in association with ectopic pregnancy. We have seen 13 patients with no interval bleeding, whose last menses were more than 35 days prior to operation for ectopic pregnancy. The endometria of 3 of these, though intact, failed to display either decidua or the atypical alteration. Other patients began uterine bleeding before the decidua had had time to develop and the endometrium was thereby deprived decidua and the atypical hyperplastic changes. That these atypical changes are produced by increased hormones seems well established, but other unknown factors may be present. It has been reported only in the presence of trophoblastic tissue. It is possible that it is simply a stage through which endometrium progresses in all normal pregnancies. This possibility is suggested by our observations and by the reports of others. 10, 12, 18 A study of multiple blocks from normally pregnant uteri would be quite revealing.

The atypical reaction also occurs in endometrium displaced from the uterine cavity as in endometriosis. Since this displaced endometrium does not always respond adequately to hormones, the atypical reaction is inclined to be less frequent. A similar atypical hyperplastic response is also occasionally noted in the tubal epithelium associated with ectopic pregnancy. There are some differences but the principal alterations are just as marked.

Heretofore, most authors have been impressed with the value of finding atypical endometrium without villi upon curettage as an aid in the diagnosis of ectopic pregnancy. We feel that this has been overemphasized since simple culdocentesis will undoubtedly produce a positive diagnosis in a much higher percentage of cases and will not run the risk of disturbing an early uterine pregnancy. On the other hand, these atypical features must be kept in mind and differentiated from malignant changes so that cancer therapy will not be instituted upon the patient with an ectopic pregnancy. There are sufficient criteria to differentiate the two. Endometrial cancer does not share in secretory or decidual response, nor is there secretory debris in the lumina of malignant glands. There are no abnormal mitoses in the atypical reaction associated with ectopic pregnancy, nor does the epithelium invade the stroma. Then, in the atypical change as described by Arias-Stella and as we have seen, the cytoplasm contains large secretory vacuoles, and its appearance is foamy. Of course, the age and type of patient as well as careful history and adequate examination will generally lead one to the proper diagnosis.

Conclusions

1. One hundred forty-four patients with ectopic pregnancy were treated by operative procedures including hysterectomy from Jan. 1, 1952, through Dec. 31, 1958, on the Tulane Service. The atypical changes as described by Arias-Stella were found in the endometria of 87 (60 per cent) of these. In 9 cases the changes were of marked degree. It is suggested that these changes might be found in the endometria in all normal pregnancies if enough sections were made at the proper time.

2. The atypical reaction was also present in 5 of the lesions in 17 patients with adenomyosis or ovarian endometriosis.

3. A similar atypical response was noted in the epithelium of 19 of 116 Fallopian tubes studied.

4. The interrelationships of villus degeneration, corpus luteum regression, desquamation of the endometrium, and the presence

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of decidua, and the atypical reaction has been shown.

5. The importance of these changes seems to lie in the fact that they may be misinterpreted to represent adenocarcinoma and may lead to false-positive cytologic findings for the patient with an ectopic prenancy.

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Cellular atypia in endometrial glands (Arias-Stella reaction) as an aid in the diagnosis of ectopic pregnancy

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The clinical diagnosis of ectopic pregnancy is not infrequently difficult. An early stage of tubal pregnancy, an atypical history, the masking of the findings by concomitant pelvic disease, and the failure of ancillary aids such as culdocentesis, culpotomy, or culdoscopy are factors which can obscure the diagnosis. The role of the pathologist in the preoperative diagnosis is confined to relatively few cases because the urgency of the condition frequently precludes preoperative curettage. When curettage is performed, the operator is too often content with only gross examination of curettings and does not even await the pathology report.

In puzzling cases the role of the pathologist is twofold: (1) establishment of the diagnosis of uterine pregnancy by the finding of chorionic villi and (2) alerting the clinician to the possibility of an extrauterine generation by reporting the absence of chorionic villi. If curetted material exhibits a decidual reaction, the possibility of an ectopic pregnancy is enhanced. However, the statement that the absence of chorionic vill in the presence of a decidual reaction bespeaks extrauterine gestation is far from

absolute. Romney, Hertig, and Reid¹ and Malkasian and associates² reported decidual reaction in only 19.1 and 18.9 per cent of endometria from patients with ectopic pregnancy. Pildes and Wheeler,³ in a smaller series, however, report decidual reaction in 60 per cent. Therefore, if one is guided solely by the presence of decidua, evidence of pregnancy will not be found in about 40 to 80 per cent of patients with tubal gestation.

In 1954 Arias-Stella⁴ emphasized another histologic feature of endometrium valuable in determining the presence of pregnancy. Although his publication is relatively recent, we may, with profit, review his findings. He observed endometrial glands with enlarged cells containing enlarged, hyperchromatic and irregular nuclei. Such atypical cells appeared singly, in small groups within otherwise normal glands, or even involved all the cells of the gland. Mitotic activity was not noted. Apparent desquamation of these cells into gland lumina and loss of nuclear polarity were present. The nuclear changes were best seen in endometria with morphology consistent with the secretory or exaggerated secretory phase, but they were also encountered in the mucosa in the proliferative phase. The endometrial stroma did not share this nuclear atypia and was decidual or fibrillar in appearance.

Arias-Stella reviewed the endometrium

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Table I. Incidence of Arias-Stella reaction and decidual reaction in endometria of patients with ectopic pregnancy

	Pildes and Wheele		Freder	iksen14	Arias- an Gutie	ad	Mac Wolfe Poz	, and	To	tal
No. of cases of ectopic pregnancy	50		32		44		42			168
Absence of both decidual and Arias-Stella reac- tion	25 (5	50%)	15	(47%)	16	(36%)	11	(26%)	67	(40%)
Decidual reaction pres- ent, Arias-Stella reac- tion absent	12 (4	42%)	4	(13%)	6	(14%)	14	(33%)	36	(21%)
Both decidual and Arias- Stella reaction present	,	18%)		(22%)		(23%)		(10%)		(18%)
Decidual reaction absent, Arias-Stella reaction present	4 (8	3%)	6	(19%)	12	(27%)	13	(30%)	35	(21%)

from 182 uterine abortions, 44 trophoblastic lesions, and one tubal pregnancy. In 11 per cent of the uterine abortions and in 25 per cent of the trophoblastic lesions (choriocarcinoma, chorioadenoma destruens and syncytial endometritis) striking epithelial cellular changes as described above were encountered. The finding of similar changes in the endometrium in the single case of ectopic pregnancy was considered of great importance for it provided evidence that similar nuclear changes could result from extrauterine as well as from intrauterine gestation.

Two lines of criticism developed following this publication. Novak5 emphasized the lack of a control series of nonpregnant patients. Greene⁶ indicated that similar changes might appear in endometria of patients with persistent corpora lutea, a postulate not yet substantiated. The first criticism would now appear to be untenable, for Svensson⁷ and also Pildes and Wheeler3 were unable to find cell changes in endometria not associated with the pregnant state. Furthermore, Frederiksen8 reported on about 1,000 routine endometria from which chorionic villi were absent except for two specimens associated with hydatidiform moles. The changes described by Arias-Stella were found in 38 instances and in 12 of these an ectopic pregnancy was subsequently demonstrated. In 6 of the 12 the Arias-Stella reaction was "of considerable significance in establishing the diagnosis." The majority of the remaining 26 could definitely be ascribed to uterine abortion although routine histologic investigation did not reveal chorionic villi. It appears, therefore, that the Arias-Stella reaction is a histologic criterion of pregnancy in uterine and extrauterine sites.

In

In discussing the paper by Pildes and Wheeler both Greene and Hofmeister9 challenged the practical value of these findings as an aid in the diagnosis of ectopic pregnancy. To date, recording of cases in which Arias-Stella cells contributed to the diagnosis of an ectopic pregnancy are scarce. Reference has been made above to the 6 cases reported by Frederiksen. Brux and Vaissade¹⁰ have suggested the diagnosis of tubal gestation on this basis in 6 subsequently proved ectopic pregnancies. Berthelsen¹¹ also reported a case in which the secretory endometrium obtained by curettage contained a few Arias-Stella cells. Hysterosalpingography which was then performed indicated the presence of a left tubal pregnancy which was surgically confirmed.

To be of value as a diagnostic aid in atypical ectopic pregnancies the epithelial changes described must occur in a significant number of cases. Table I indicates that in the presence of tubal gestation with encometrium available, the pathologist can correction

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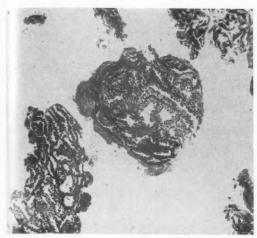


Fig. 1A. Case 1: Low power view of curettings. Note delicate, lacelike, regularly arranged intraluminal papilla into hyperplastic glands. (×16; reduced 3/7.)

rectly predict the presence of a pregnancy in 60 per cent of the cases. In two thirds the diagnosis is based on the presence of decidua. In the absence of decidua the diagnosis of pregnancy can be made in the remaining

one third by the presence of Arias-Stella cells alone.

Confounding such changes with those of endometrial carcinoma is an aspect to be emphasized. Truemner¹² reported a case in which the nuclear changes were so pronounced that hysterectomy and bilateral salpingo-oophorectomy were performed for a supposed endometrial adenocarcinoma. Case 1 in this series depicts a similar mistake. In the case of Tweeddale and Hoffman¹³ a patient with ectopic pregnancy had an endometriotic nodule in the cul-de-sac in which the nuclear atypism caused concern. Greene⁶ was similarly concerned about such a zone in the endometrium of an excised uterus from a patient with ectopic pregnancy. However, the reading of the paper by Pildes and Wheeler³ directed him from the diagnosis of possible carcinoma to one of nuclear atypism of pregnancy.

We became aware of the atypical nuclear changes described by Arias-Stella shortly after publication of his paper in August,

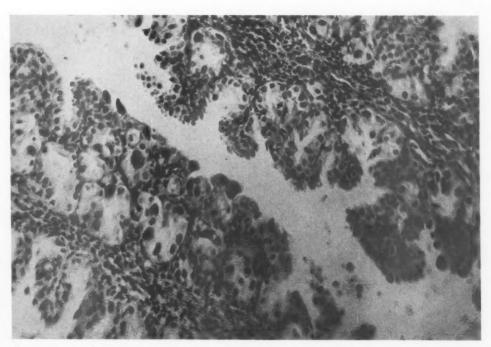


Fig. 1B. Case 1. The central cleft represents the lumen of a hyperplastic endometrial gland. Papillary projections and small "daughter" glands are present. Many, though not all, endometrial gland fining cells contain irregular, markedly enlarged and hyperchromatic nuclei. Mitoses are absent. The seeming resemblance to carcinoma is apparent. (×300; reduced ½.)

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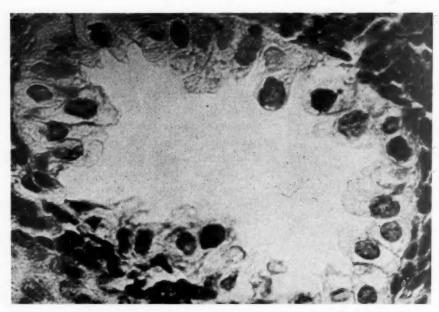


Fig. 2. Case 2. Details of endometrial cells in a single gland. All cells are enlarged. The nuclei are atypical and varied in size and staining intensity. Stratification of cells is slight. (×600; reduced ¼.)

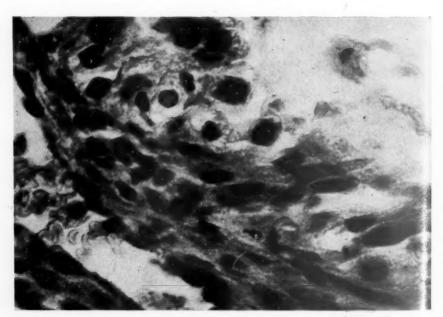


Fig. 3. Case 3. Details of nuclear changes. Hyperchromatism and irregularity in size and shape are evident. Note the irregular position of the nucleus in the cell body. The underlying stromal cells course in parallel groups beneath the epithelial lining. (×600; reduced 1/4.)

1954. Since Jan. 1, 1955, we have collected 6 instances of tubal pregnancy in which the alerrant nuclear changes within the endometrial glands proved of significance in the diagnosis. Although these represent but 4.4 per cent of the 135 tubal pregnancy specimens received in our laboratory from Jan. 1, 1955, to April 1, 1960, they obviously represent a much higher percentage of cases in which clinical diagnostic difficulties were present. Endometrial tissue was available for study in 42 of the 135 cases. In 30 of the these cases histologic study of the endometrium played no part in diagnosis because the operation had already been performed. In the remaining 12 patients the endometrium was obtained more than 48 hours prior to salpingectomy either by spontaneous expulsion of decidual tissue, as in 2 cases, or by curettage. Of these, examination revealed proliferative endometrium in 1 and decidual changes in 4. The sixth case disclosed both decidual stromal reaction and atypical epithelial changes. In the remaining 6 patients, although no decidual reaction was present, changes in the epithelial cells as described by Arias-Stella were noted and, except for one case (Case 1) which was incorrectly interpreted, they directed attention to the pregnant state. The 6 case abstracts follow.

Case reports

Case 1. Mrs. S. P., a 36-year-old white woman, was admitted to the Jewish Hospital of Brooklyn on Sept. 18, 1955, because of severe pain in the lower abdomen. This first appeared with the onset of the "menstrual period" which began on August 17. The pain persisted to the time of admission and was associated with episodes of recurrent vaginal staining and bleeding. General physical examination was unremarkable. The pelvic findings failed to reveal a mass or tenderness. Curettage was performed for suspected dysfunctional bleeding.

Grossly, the curettings consisted of several pink and gray fragments of tissue which measured up to 2 cm. in greatest dimension. The microscopy findings (Fig. 1) consisted chiefly of closely pa ked, small glands lined by cells varying in marphology from large cuboidal to irregularly rounded forms. Many contained an abundance

of clear or eosinophilic cytophasm with large, bizarre nuclei. Strikingly, nuclei in adjoining cells appeared normal. Occasional larger gland spaces presented delicate papillary infoldings. Mitoses were not noted. The stroma was scant and compact. Because of the unusual nuclear morphology, three different observers concurred in the diagnosis of endometrial adenocarcinoma in situ. Accordingly, a total hysterectomy and bilateral salpingo-oophorectomy were performed on Sept. 24, 1955. The uterus, right Fallopian tube, and right ovary appeared normal. The left ovary contained a bright yellow corpus luteum 1.5 cm. in diameter. A hemorrhagic ovoid mass 2 cm. in length was present in the mid-portion of the left Fallopian tube. On section a tubal fetal sac containing an embryo 4 mm. long was found in its central portion. Microscopically, wellpreserved chorionic villi were present in the blood clot forming the mass. In several endometrial glands nuclear changes similar to but less marked than those in the curetted material were noted.

Case 2. Mrs. F. K., a white woman, aged 36 years, was seen in the Outpatient Clinic of The Jewish Hospital on Nov. 19, 1957, because of irregular vaginal bleeding. The last normal menstrual period occurred early in October. The ensuing "period" appeared at the expected time late in October but irregular spotting and bleeding persisted until admission to the hospital on November 20. Pelvic examinations in the clinic and on admission to the hospital were negative. The clinical diagnosis was menometrorrhagia secondary to either endometrial hyperplasia or an endometrial polyp. Curettage was accordingly performed the day following admission and the patient was discharged 48 hours later.

A moderate amount of endometrial tissue was obtained upon curettage. The endometrium was of secretory type and contained foci in which the gland lining cells were enlarged by an abundance of clear cytoplasm; occasional nuclei stained deeply and were of irregular shape and moderately enlarged (Fig. 2). They were reported, after the patient's discharge from the hospital, as containing atypical nuclear changes of endometrial gland lining cells and absence of trophoblastic elements. An opinion of possible tubal pregnancy was made.

Four days after discharge the patient sought readmission because of the sudden onset of right lower quadrant pain and continued vaginal bleeding. On pelvic and rectal examination a tender mass 2 cm. in diameter was felt in the

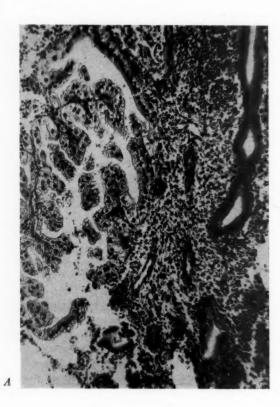
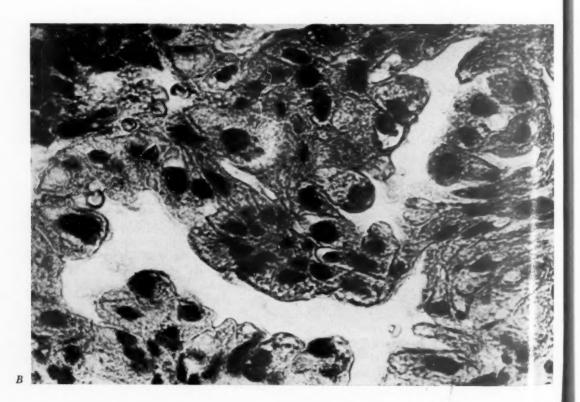


Fig. 4. Case 4. A, The gland on the right in the proliferative phase contrasts sharply with the hypertrophied papillary gland and its clear cells on the left. Decidual changes are lacking. (×300; reduced %.) B, Details of nuclear changes in endometrial gland lining cells from another area. Cell enlargement and stratification are marked. Note intensity of nuclear stain and variation in nuclear size and shape. (×600; reduced ½.)



ri ht cul-de-sac. At laparotomy the following d v the right tube was found to contain an unriptured tubal pregnancy and was removed. The pesence of placental tissue within the tube was e afirmed on microscopy examination.

Case 3. W. M. J. a 42-year-old Negro woman, was admitted to The Jewish Hospital of Brooklyn on May 4, 1958, because of menometrorrhagia. Menses had been normal until February, 1958, when excessive vaginal bleeding was followed by spotting for 1 or 2 weeks. Whether or not a normal menstrual period occurred in March is not known. The present episode of bleeding commenced 2 weeks before admission and was associated with lower abdominal cramps. On pelvic examination the uterus was thought to be slightly enlarged, and questionable thickening and slight tenderness were noted in the left fornix. However, on repeat pelvic examination with the patient anesthetized prior to curettage on the second hospital day, uterine size was found to be normal and no adnexal masses were discernible. Curettage yielded a moderate amount of tissue.

Upon histologic examination the endometrium was found to consist, for the most part, of tortuous secretory glands in a partly loose and partly compact stroma. In some areas there were groups of enlarged glands lined by enlarged epithelial cells with abundant clear or eosinophilic cytoplasm and enlarged, deeply staining, and occasionally irregularly shaped nuclei. Decidual reaction and trophoblastic elements were not present (Fig. 3).

Because of the pathologist's suspicion of the pregnancy state, the patient, who had already been discharged, was readmitted for further study. An Aschheim-Zondek test was reported as positive. Culdoscopy was performed and was regarded as a failure inasmuch as the distal three fourths of the left tube was not visualized; a small hemorrhagic mass noted in the right mesosalpinx was regarded as a varix. An Aschheim-Zondek test 3 days after culdoscopy was reported as negative and the patient was again discharged to the clinic. Several subsequent A chheim-Zondek tests were also reported as n gative. Vaginal bleeding continued. On June 8 four weeks after culdoscopy, examination revaled a cystic mass about 8 cm. in diameter in the right adnexal area. Laparotomy was performed. The mass consisted of a small, simple right ovarian cyst with the tube and ovary on that side united by adhesions. The wall of the mid-portion of the tube contained a small, firm, dark blood clot in which several degenerated chorionic villi were seen on microscopic study.

Case 4. M. C., a 36-year-old Negro woman, reported to the Outpatient Clinic of The Jewish Hospital of Brooklyn on Jan. 28, 1960, because of vaginal bleeding. Her last normal menstrual period began Dec. 5, 1959. On January 4 an episode of vaginal spotting that lasted for 36 hours was noted. On January 11 bleeding occurred and was continued to the time medical advice was sought. The bleeding was regarded as heavy from January 11 to January 18 and of lesser amount thereafter. Upon pelvic examination the uterus was found to be of normal size and shape. Slight tenderness and thickening were noted in the right adnexal region. The patient was instructed to return in one week, and at that visit she still complained of vaginal bleeding. An endometrial biopsy was performed, 100 mg. of progesterone was given, and she was told to return in 10 days.

The endometrial biopsy specimen consisted of small portions of mucosa composed of somewhat tortuous glands in a moderately loose stroma. In several foci, however, the glands appeared dilated, more closely packed, and lined by tufts of enlarged cells with clear or eosinophilic cytoplasm and occasionally enlarged nuclei, some of which were distinctly atypical (Fig. 4). Decidual tissue and trophoblastic elements were absent.

Inasmuch as these histologic findings indicated the presence of an ectopic pregnancy, the patient was admitted to the In-Patient Department of The Jewish Hospital for further study. Culdoscopy performed on the day of admission, February 8, revealed the presence of a hemorrhagic mass distending the lateral third of the left Fallopian tube. The next day an Aschheim-Zondek test was reported as positive and a left salpingectomy was performed. The lateral half of the left tube was distended with blood clot in which, upon microscopy examination, both well-preserved and poorly preserved chorionic villi were noted.

Case 5. Mrs. H. G., a 31-year-old white woman, was admitted to The Jewish Hospital of Brooklyn on Aug. 11, 1955, because of vaginal bleeding. Her last normal menstrual period began May 28, 1955. From July 2 through July 17 vaginal bleeding was noted. Bleeding of varying degrees resumed July 27 and was attended by left lower quadrant pain. An Aschheim-Zondek test on August 1 was reported as positive. She

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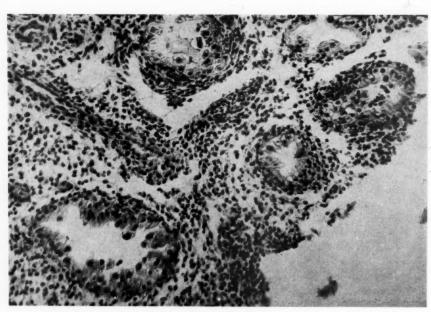


Fig. 5A. Case 5. Involved glands seemingly present secretory morphology. Note the tendency of abnormal nuclei to lie near the gland lumen. Decidual reaction is absent. (×300; reduced 1/4.)

was admitted to The Jewish Hospital on August 11. On pelvic examination the cervix was closed and insensitive and the uterus was slightly enlarged. Adnexal masses were not palpated and

adnexal tenderness was absent. The clinical impression was one of early missed abortion or possible ectopic pregnancy. Curettage was performed the day after admission and upon examination

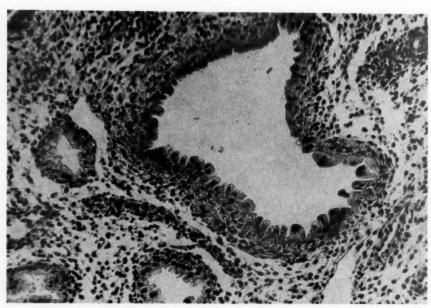


Fig. 5B. Case 5. Marked nuclear changes are seen in greatest degree in one portion of the involved, dilated gland. Not all cells are involved. (×300; reduced 1/4.)

osed un er anesthesia it was again noted that no ad exal mass was palpable. She was discharged 48 hours later.

The curettings were moderate in amount. They consisted of secretory type endometrial glands in a loose stroma. In several areas groups of clands were enlarged and lined by multilayered epithelium consisting of irregularly shaped large cells with an abundance of clear cytoplasm, and, in many, markedly atypical nuclei were present. The atypia appeared most marked in cells close to or actually shed into the lumen. Stromal decidualization was not present and trophoblastic elements were not noted (Fig. 5).

The Aschheim-Zondek test was then repeated and again found to be positive. She was readmitted on August 17 for further study. The following morning a definite thickening associated with minimal tenderness was noted in the left adnexal area on pelvic examination. At laparotomy that afternoon the left tube was dilated and surrounded by several layers of old blood. Histologic study revealed the presence of well-preserved chorionic villi in the tubal wall.

Case 6. Mrs. M. P., a white woman, aged 35 years, was admitted to The Jewish Hospital of Brooklyn on June 22, 1959, because of vaginal bleeding and slight right lower quadrant pain of 5 days' duration. Her last normal menstrual period had begun April 14, 1959, and an Aschheim-Zondek test prior to admission was positive. On pelvic examination the uterus was slightly enlarged, and a small, slightly tender, mobile cystic mass, 3 cm. in diameter, was palpated in the right adnexa. The clinical impression was one of incomplete abortion and a cystic corpus luteum of pregnancy. Curettage was performed and the patient was discharged.

Upon histologic examination the endometrium was found to lack decidual reaction or trophoblastic elements. It consisted chiefly of small, straight tubular glands of proliferative type in a compact stroma. However, occasional glands (Fig. 6) were lined by a single row of larger cells with clear cytoplasm and distinctly enlarged nuclei. The possibility of an ectopic pregnancy was suggested to the patient's physician and it was decided to repeat the Aschheim-Zondek test. When this was reported as positive she was readmitted for culdoscopy studies. Pelvic examination revealed that the adnexal mass was still present, but the patient was asymptomatic. A distended and hemorrhagic right tube was clearly

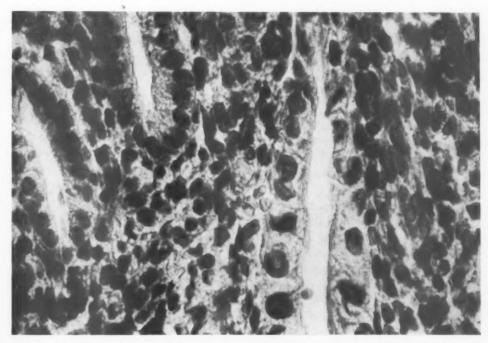


Fig. 6. Case 6. Glands on the left are of normal interval type. In the gland on the right the cells are pale and enlarged; the majority of the nuclei are pale and enlarged but several stain deeply. (×600; reduced 1/6.)

visualized with the culdoscope. Salpingectomy confirmed an in situ ectopic pregnancy which was histologically confirmed by the finding of well-preserved chorionic villi.

Comment

In the first 4 cases the pregnant state was not suspected on clinical grounds. In Cases 2, 3, and 4 the histologic examination of curettings first indicated this status despite the absence of decidual reaction in the endometrial stroma. The basis for the diagnosis of a pregnancy status rested solely upon the finding of atypical nuclear changes in endometrial gland lining cells as described by Arias-Stella. In Cases 5 and 6 the presence of pregnancy was known at the time of admission. However, the positive clinical diagnosis of ectopic pregnancy was not made initially as an adnexal mass was not palpable in Case 5 and was misinterpreted in Case 6. In both patients the presence of atypical nuclear changes alone served to alert the pathologist and clinician to the possibility of tubal pregnancy.

The single clinical factor responsible for the difficulty in clinical diagnosis in this group of cases was the lack of an enlarged adnexal mass (Cases 1 to 5, inclusive) or its misinterpretation (Case 6). In Cases 2, 3, and 5 an adnexal mass was not palpated initially. It was only upon subsequent observation with further enlargement of the tubal pregnancy that the correctness of the original diagnosis was ultimately proved by operation. In Cases 1 and 4 the tube containing the ectopic gestation was never palpable.

From these experiences the following program is recommended in patients curetted because of vaginal bleeding if the Arias-Stella changes are found and no trophoblastic elements are encountered:

1. Remaining, nonprocessed tissue is

further examined for undetected chorion celements.

2. If these are lacking, a biologic test for pregnancy is performed and the patient rexamined. If the biologic test is positive and no adnexal mass is present, culpotomy or culdoscopy is performed to exclude ectopic gestation. Cases 4 and 6 were disclosed by this regime.

The mechanism of the Arias-Stella reaction is not discussed here. However, the variation in frequency of these atypical cells may be explained by the varied preservation and quantitative hormonal output of chorionic tissue at the tubal site and the corpus luteum of pregnancy. These features will be evaluated in a further study of a retrospective series now in preparation.

Summary and conclusions

- 1. The literature pertaining to the Arias-Stella reaction in ectopic pregnancy is reviewed.
- 2. Six cases of ectopic pregnancy in which the clinical diagnosis was difficult and in which atypical cellular and nuclear changes were present in nondecidual endometria are reported.
- 3. In 4 instances the presence of the cellular changes was the first evidence of the pregnant state. The histologic interpretation was correct in 3 and, in 1 instance, the changes were so marked that an erroneous diagnosis of adenocarcinoma was made. In 2 patients known to be pregnant at the time of admission the presence of these changes led to continued observation, and a tubal pregnancy was ultimately proved to exist.
- 4. The presence of the Arias-Stella reaction in endometrium is an additional aid in the diagnosis of obscure and atypical cases of ectopic pregnancy.

We are grateful to Mr. Marvin Ehlin and Miss Esther Torres for the photomicrography.

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The suspected ectopic pregnancy

A review of 500 cases

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The diagnosis of ectopic pregnancy is difficult. The risk to the patient from an undiagnosed ectopic pregnancy is great. For these reasons the astute clinician must often make the tentative diagnosis of "possible ectopic pregnancy" until his suspicion can be substantiated or eliminated by further evaluation of the case. The purpose of this paper is to present the data obtained from the study of 500 cases in which the diagnosis of ectopic pregnancy was entertained, with varying degrees of conviction, at the time of the patient's admission to the Sloane Hospital for Women.

Source of material

Upon admission of a patient to the Sloane Hospital for Women, a secretary fills out a card upon which the patient's name, unit number, and other pertinent information are inscribed. The tentative diagnoses of the admitting physician are copied from the chart and recorded here together with any additional diagnoses made during the patient's hospital stay. These cards were used as the source of case selection for this study. Whenever a card indicated that the diagnosis of ectopic pregnancy had been considered. corresponding the chart examined. If the case history confirmed the fact that this diagnosis had been seriously

entertained, as was almost invariably true, the case was included in the series, regardless of what the ultimate diagnosis proved to be. th

Unfortunately, through the years, these cards have not been used for research purposes and so they have not been scrupulously saved. For this reason the cases reported in this paper are not entirely consecutive; on the other hand, they are in no way purposefully selective. Actually they consist of all of the cases between 1946 and 1956, inclusive, except for 1952 and half of 1953, for which years the cards were lost. A few cases were added, without selection, from the 1957 files in order to round out the series at 500. Only ward cases were included, for, in contrast to the rule in private practice, the suspicion of extrauterine pregnancy in these cases invariably leads to hospitalization.

The degree of diagnostic certainty in the mind of the admitting doctor, usually a member of the house staff, was exhibited by the phraseology of his clinical impression. Sometimes this was expressed without qualification (e.g., "ruptured ectopic pregnancy"); more often other diagnostic possibilities were listed (e.g., "pelvic inflammatory disease or ectopic pregnancy"); frequently the likelihood of an ectopic pregnancy, though remote, seemed sufficiently inescapable to warrant hospital admission (e.g., "hemorrhagic corpus luteum, rule out ectopic pregnancy"); and occasionally the diagnosis of ectopic pregnancy was not even

From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women. rue,

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co isidered until after the patient's admission to the ward.

Crude diagnostic analysis

In 209 or 40 per cent of the 500 cases there was ultimate histologic proof of the presence of an ectopic pregnancy. The precise diagnoses eventually reached in the nonectopic* group are discussed in a later section. A crude diagnostic breakdown of all 500 cases is presented in Table I. Here the case material is divided among "ectopic" and "nonectopic" and considered in light of the diagnostic measures which were used to prove or disprove the presence of ectopic pregnancy. A more detailed description of these eight categories follows:

Group I consists of the 65 cases in which the diagnosis of ectopic pregnancy was obvious from the historical data obtained and the physical examination performed at the time of hospital admission. In none of these cases was a second diagnosis considered. Twenty-five of these patients exhibited evidence of vascular collapse. All but 2 were operated upon within 24 hours of admission.

Group II consists of 16 cases of unruptured ectopic pregnancy. No free blood was encountered in the peritoneal cavity when these patients were operated upon. It seemed proper to consider these cases separately, since the emphasis of this paper is upon the differential diagnosis of ectopic pregnancy and the diagnostic features of unruptured ectopic pregnancy are somewhat distinct from those cases which are associated with hemoperitoneum.

Group III consists of the 124 cases of runtured ectopic pregnancy which proved to be diagnostic problems. It is not surprising that this group comprises 65 per cent of the entre number of ruptured ectopic pregnancies which were diagnosed preoperatively. The correct diagnosis was reached before operation on the basis of history and physical findings alone in 17 cases; with additional relance upon laboratory tests (including

serial hemoglobin determinations and pregnancy tests) and clinical course under observation in 55 and with the further help gained from minor operative procedures (curettage, colpotomy, colpocentesis, and/or culdoscopy) in 52.

Group IV consists of 4 ectopic pregnancies, the correct diagnosis of which was not entertained prior to laparotomy. The preoperative diagnosis in 2 of these cases was fibromyomata uteri; in 1 it was pelvic inflammatory disease. In the fourth case exploration was carried out on the general surgical service with the preoperative diagnosis of appendicitis; a member of the gynecologic service was called in after the ectopic pregnancy had been found and the patient was subsequently transferred to the obstetric floor.

Group V consists of the 46 cases in which the preoperative diagnosis of ectopic pregnancy proved at laparotomy to have been in error. This type of case, which must inevitably be associated with any series of ectopic pregnancies, is rarely reported in the medical literature. It seems rather alarming that almost one in every 10 patients in this series underwent laparotomy for an ectopic pregnancy which did not exist, but perhaps this in part explains the fact that there were no deaths in the series from failure in diagnosis or delay in treatment.

Group VI consists of the 50 cases in which the possibility of ectopic pregnancy was ruled out with the help of minor operative procedures such as curettage and colpotomy.

Table I. Crude diagnostic analysis of 500 "possible ectopic pregnancies"

I.	Ectopic—obvious	65)
II.	Ectopic—unruptured	16	
III.	Ectopic-diagnostic		209 ectopic
	problems	124	
IV.	Ectopic—unsuspected	4)
V.	Nonectopic—laparotomy	46)
VI.	Nonectopic-minor		
	operative procedures	50	291 non-
VII.	Nonectopic—clinical		ectopic
	grounds	156	
VIII	Nonectopic—obvious	39	J

The words "ectopic" and "nonectopic" are loosely used in this paper for the purpose of brevity.

Table II. Delay in diagnosis

Doctor to ad- mission (average) (days)		Group	Admission to diagnosis (average) (days)
2.2	I.	Ectopic—obvious	1
7.4	II.	Ectopic—unruptured	5.4
6.5	III.	Ectopic—diagnostic problems	3.4
16.8	IV.	Ectopic— unsuspected	2.5
3.1	V.	Nonectopic— laparotomy	3.0
4.0	VI.	Nonectopic—minor operative pro-	
		cedures	4.4
2.3	VII.	Nonectopic— clinical grounds	3.5
	VIII.	Nonectopic—	
		obvious	1
4.0		All groups	2.9

Group VII consists of the 156 cases in which the possibility of ectopic pregnancy was ruled out on clinical and laboratory grounds alone.

Table III, A. Comparative incidence of various signs, symptoms, and laboratory tests

	209 ectopics (%)	252 nonec- topics* (%)
Chief complaint: pain	89	88
Chief complaint: bleeding	11	12
Shoulder pain	-17	6
Vaginal bleeding	82	57
Shock and/or fainting	33	11
Abdominal tenderness	89	85
Definite adnexal mass	43	44
Indefinite adnexal mass	23	33
No adnexal mass	34	23
Amenorrhea 40 to 90 days	74	55
Uterus 6 weeks' size or less with- out fibroids	95	89
Temperature less than 101° F.	98	98
Hemoglobin less than 14.1 Gm.	97	87
White blood count less than 25,000	98	99
Erythrocyte sedimentation rate	36	33
less than 50 mm. per hour	89	89
Positive pregnancy test	89	46

^{*}Excluding the cases in Group VIII.

Group VIII consists of the 39 cases in which it was obvious immediately after admission to the hospital that the admitting physician's suspicion of ectopic pregnancy could not be substantiated. Although they contribute very little to the educational aspects of this study, they are nevertheless included for the sake of completeness in that they do share the denominator common to the other cases in the series, ectopic pregnancy having been suspected at one time or another (although it was not suspected preoperatively in the 4 cases in Group IV).

Review of the 500 cases in this series has yielded a vast amount of data, much of which duplicates those recorded in previous reports on this subject. It is proposed, therefore, to limit the following presentation to the findings which stem rather directly from the fact that this study includes all of the cases in which the diagnosis of ectopic pregnancy was considered. No worthwhile purpose is to be served, for example, by describing the classical picture of ectopic pregnancy encountered in Group I; there is more to be gained from a study of those cases in which a diagnosis was reached with difficulty. If the following exposition appears to this extent disconnected, it is largely due to this attempt to select only the more significant data from this particular case material.

Delay in diagnosis

The time lapse between the patients' first appearance in the clinic and their admission to the hospital is depicted in the left-hand column of Table II. Forty-one per cent of the ectopic group and 37 per cent of the non-ectopic group were sent home from the clinic at least once before their admission to the hospital. Sixty per cent of the entire series were admitted to the hospital immediately after their first clinic visit; the delay exceeded a week in 14 per cent.

The time lapse between admission to he hospital and definitive diagnosis is shown in the right-hand column of Table II. The final diagnosis was made within 24 hours in 50 per cent of the entire series; the delay exceeded 3 days in 27 per cent.

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Table III, B. Comparative incidence of various signs, symptoms, and laboratory tests

i.	Ectopic pregnancy (209) (%)	Pelvic in- flammatory disease (56) (%)	Abortion (35) (%)	No preg- nancy or pelvic in- flammatory disease (88) (%)	Intrauterine pregnancy (73) (%)
Chief complaint: pain	89	87	74	84	99
Chief complaint: bleeding	11	13	26	16	1
Shoulder pain	17	14	9	2	1
Vaginal bleeding	82	66	94	53	29
Shock and/or fainting	33	13	57	11	82
Abdominal tenderness	89	97	72	92	91
Definite adnexal mass	43	55	49	57	58
Indefinite adnexal mass	23	16	14	16	20
No adnexal mass	34	29	. 37	27	22
Amenorrhea 40 to 90 days	74	36	66	38	79
Uterus six weeks' size or less, without					
fibroids	95	100	91	95	73
Temperature less than 101° F.	98	93	100	99	96
Hemoglobin less than 14.1 Gm.	97	91	80	87	93
White blood count less than 25,000	98	100	100	100	99
Erythrocyte sedimentation rate less					
than 50 mm. per hour	89	78	92	98	86
Positive pregnancy test	89	5	66	4	96

The total average delay between first clinic visit and ultimate diagnosis or treatment for the entire series was 6.6 days.

Signs and symptoms

The comparative incidence, for the ectopic and the nonectopic groups, of some of the various signs, symptoms, and laboratory findings commonly associated with ectopic pregnancy is shown in Table III, A. Actually, this table represents a condensation of our repeated efforts to devise an artificial formula by which the ectopic and nonectopic cases could be retrospectively differentiated. With each individual sign or symptom, no matter how its limits were manipulated (e.g., by lowering the sedimentation rate to 25 or raising it to 100), it was found impossible to exclude a significant proportion of the nonectopic group without sacrificing a considerable number of the ectopic group as well. As presented, these criteria are met by nearly all of the ectopic group, but at the same time they are met by the nonectopic group in almost identical proportions. The only significant exception to this is the comparative incidence of positive pregnancy tests.

In the differential diagnosis of individual cases of "possible ectopic pregnancy," there is often only one other syndrome which warrants serious consideration. The most common alternative possibilities are pelvic inflammatory disease, threatened and incomplete abortion of an intrauterine pregnancy, and intrauterine pregnancy complicated by degenerating fibromyomas, ovarian cysts, or the like. Table III, B shows the comparative incidence of the same signs and symptoms among patients with these specific final diagnoses. There is, of course, greater contrast in the frequency of some of these signs and symptoms between the ectopic group and these other individual syndromes than there is between the ectopic and the nonectopic groups when the latter is considered as a collective entity; but, even so, this difference is not sufficiently striking to facilitate diagnosis in the great majority of individual cases. Again, the only sign which is of undeniable significance in this regard is the pregnancy test.

Table IV. Reasons for laparotomy in 16 cases of unruptured ectopic pregnancy

Curettage for "menometrorrhagia" or	
"abortion" yielded decidua only	6
Culdoscopy for suspected ectopic	
pregnancy	4
Laparotomy for suspected ectopic preg-	
nancy (3 following curettage; 1 following	
colpotomy)	5*
Laparotomy for "unruptured ectopic	
pregnancy"	1

*One associated with hemoperitoneum from ruptured corpus luteum.

Table V. Ultimate diagnoses in 46 instances of laparotomy for erroneous preoperative diagnosis of ectopic pregnancy

Intrauterine pregnancy with fibroids, ovarian	1
cysts, etc.	13
Pelvic inflammatory	Unnecessary (33)
disease	10
Ovarian cysts, fibroids, adhesions	10
Hemorrhagic corpus	1)
Hemorrhagic follicle cyst	Possibly necessary
Gangrenous hydatid of	(3)
Morgagni	1)
Acute appendicitis	2)
Ruptured corpus luteum	3
Hematosalpinx, cause undetermined	4 Necessary (10)
Hemoperitoneum, cause undetermined	1

Unruptured ectopic pregnancies

Group II, unruptured ectopic pregnancies, merits brief special consideration with regard to how the diagnosis was reached in these 16 cases. This material is summarized in Table IV.

In 6 of these cases curettage was performed for "metrorrhagia" or "incomplete abortion" and the curettings, to the operators' surprise, revealed decidual tissue only. The diagnosis of ectopic pregnancy had not been entertained prior to the report from the pathology laboratory.

In 4 instances, culdoscopy was done to verify the suspicion of ruptured ectopic pregnancy and this procedure enabled the operator to visualize an intact tubal gestation.

On 5 occasions laparotomy was performed with the preoperative diagnosis of ruptured ectopic pregnancy, this impression having been reached on the basis of curettage (three times), colpotomy immediately prior to abdominal incision (one time), or coincidental hemoperitoneum due to a ruptured corpus luteum (one time).

Among the 255 major operations in this series there was only one in which a preoperative diagnosis of unruptured ectopic pregnancy was substantiated. It appears, therefore, that the preoperative diagnosis of ectopic pregnancy is virtually impossible before the extravasation of blood into the peritoneal cavity.

Only 50 per cent of these patients complained of abdominal pain, compared to 96 per cent of those with ruptured ectopic pregnancies. All of them had noted some vaginal bleeding. As noted above, minor operative procedures were necessary to establish the diagnosis of all but one of the cases of unruptured ectopic pregnancy; these procedures were done in only 30 per cent of the cases of ruptured ectopic pregnancy.

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Diagnostic problems

There is little to be gained from a detailed analysis of the 124 cases which constitute Group III (cases presenting diagnostic problems but proved to be ectopic pregnancies), for this is the group about which a plethora of medical articles has already been written. The signs and symptoms of the entire ectopic group have been presented; the accuracy of the pregnancy test and of the minor operative procedures is discussed below.

A few isolated facts are noteworthy. A fall in the hemoglobin value and the sudden appearance of vascular collapse under observation contributed significantly to the diagnosis in 19 cases and 2 cases, respectively. A decidual cast was noted in only one instance.

With regard to the ectopic group as a whole, it might be appropriate to mention here that the preponderance of ectopic gesta-

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ions in the right tube, so generally reported¹ and poorly understood, was confirmed. Fifty-three per cent were located in the right tube, 47 per cent in the left. In 64 cases a prediction was expressed in the chart as to which tube harbored the pregnancy; these predictions proved correct only 75 per cent of the time.

Erroneous preoperative diagnoses

The preoperative impression of ectopic pregnancy was not confirmed in the 46 cases of Group V. The ultimate diagnoses in these cases are outlined in Table V.

In 33 of these cases no other condition was found at the time of laparotomy which would justify the operation; hence, these 33 operations were completely unnecessary.

In 3 other cases, the disease processes encountered at operation might be regarded as sufficient indication for operation.

In the remaining 10 cases, although the preoperative diagnosis proved to be incorrect, the operation could be justified on other grounds. The last 5 cases listed in this table might indeed have been ectopic pregnancies which were not discovered by the pathologist, but no case was considered to be an ectopic pregnancy in this series unless the presence of ectopic chorionic villi was demonstrated histologically.

It might be worth while here to make particular reference to the pregnancy test as it relates to these 46 diagnostic errors. Of the 5 cases just mentioned, which might possibly have represented ectopic gestation, pregnancy tests were done in 3. The test was positive in one case, negative in another, and positive once and negative when repeated in the third. There is little point in commenting further on these 5 cases, for the diagnosis is obscure and the significance of the pregnancy tests is therefore debatable. It mong the remaining 41 diagnostic errors, analysis of the pregnancy tests reveals the following:

1. There was one false-positive result, which was partly responsible for the error in ciagnosis.

2. There were 4 positive results which

were associated with intrauterine pregnancies, and there were 8 other cases in which a pregnancy test was not done but in which the results would presumably have been positive because of the presence of an intrauterine pregnancy.

3. There were 10 cases in which laparotomy was performed in spite of negative pregnancy tests; 16 others in which pregnancy tests were not performed but in which the results would presumably have been negative had they been done; one in which the results of the test were equivocal and another in which the results of two tests were

Table VI. Ultimate diagnoses in nonectopic Groups VI and VIII

	Group VI	Group VII
Pelvic inflammatory disease	7	37
Intrauterine pregnancy with complications	10	50
Threatened, incomplete, or complete abortions	10	23
No pregnancy, no pelvic inflam- matory disease (ovarian cysts,		
metrorrhagia, etc.)	23	46

Table VII. Accuracy of cul-de-sac procedures

20 colpocenteses $\bigg\{$	15 correctly positive 2 correctly negative 3 false negative	}	85%
32 culdoscopies {	9 correctly positive 17 correctly negative 3 unsuccessful 1 false positive 2 false negative	}	81%
42 colpotomies {	23 correctly positive 13 correctly negative 4 inconclusive 2 false positive	}	86%

Table VIII. Interpretation of the curettings of 69 cases of ectopic pregnancy

Decidua	50 (73%)
Proliferative endometrium	10
Secretory endometrium	4
No tissue	4
Specimen lost	1

contradictory, in both of which cases further tests should have yielded negative results.

In summary, the pregnancy tests contributed to the misdiagnoses in 2 cases, they should have led to a more accurate diagnosis in the 10 cases in which the results were negative, and they might have led to a more accurate diagnosis in 18 other instances had they been performed at least once and repeated if the results were unclear. At least 26 and possibly 29 of these 41 misdiagnoses might have been avoided if pregnancy tests had been performed and their results properly interpreted and heeded.

Ultimate diagnoses in the nonectopic group

The final diagnoses of Group V are presented in Table V. The final diagnoses in Groups VI and VII are presented in Table VI. Combination of the figures in the two tables reveals that among these 252 nonectopic cases the final diagnosis was: pelvic inflammatory disease in 21 per cent; intrauterine pregnancy with complications in 29 per cent; threatened, incomplete, or complete abortion in 13 per cent; and some other condition in 37 per cent.

It was pointed out above that, despite laparotomy, the possibility of an ectopic pregnancy could not be completely ruled out in 5 cases. It must be borne in mind that this possibility was ruled out on clinical grounds only in the 156 cases in Group VII, and by minor operative procedures in the 50 cases in Group VI. It is reasonable, therefore, to wonder whether at least a few of the cases in these two groups did not in fact represent unrecognized ectopic gestations.

Accuracy of the cul-de-sac procedures

Many vigorous assertions have been made in the obstetric literature as to the efficacy of the cul-de-sac procedures in the diagnosis of ectopic pregnancy. In the experience of different clinicians, one method invariably proves superior to the others.²⁻⁶ As can be seen from Table VII, in this series these tests proved approximately equal with respect to their reliability and their limitations.

Interpretation of the curettings

Curettage was performed in 69 of the 209 cases of ectopic pregnancy. The histologic interpretation of the curettings is presented in Table VIII. In addition, it is noteworthy that there was almost no correlation between the histologic picture and the duration of the amenorrhea or the duration of the abdominal pain. The curettings were decidual in all cases in which there had been no vaginal bleeding (6 cases) or in which the bleeding had been scant and of less than 8 days in duration (7 cases).

It is almost irresistible for the operator to guess whether the curettings are decidual or not. In this series these guesses proved to be wrong 59 per cent of the time.

The pregnancy test

The pregnancy test used in this study was the 24 hour mouse hyperemia test described by Berman.⁷⁻⁸

It is commonly held that pregnancy tests are unreliable in the differential diagnosis of ectopic pregnancy.⁴ The results of this series indicate not only that the pregnancy test is reliable but also that it is the single most valuable means we have to solve these diagnostic problems. Since the differential diagnosis lay between ectopic pregnancy and some nonobstetric condition in 232 of the 392 cases in which the diagnosis was unclear, the importance of a reliable pregnancy test is obvious.

Ectopic pregnancies. As indicated in Table IV, A, pregnancy tests were performed in 86 of the 209 cases of ectopic pregnancy. The results were positive in 75 or 87 per cent. In 9 cases the results were negative; in 2 cases the results of repeated tests were contradictory.

Among the 11 cases associated with negative tests, 2 were explained by the absence of viable chorionic villi on examination of the tubal contents; only ghost villi were found, but of course this explanation was no help to the clinician and, so these results must be regarded as false positive. Three other negative results can be attributed of technical errors, in that the mice were

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examined after only 6 hours in 2 cases and after 64 hours in one. The remaining 6 were in association with old second trimester ectopic gestation.

Among the 209 ectopic pregnancies in this series, the interval between the last menstrual period and the performance of the pregnancy test exceeded 95 days in 11 cases. The pregnancy tests were accurate in only 33 per cent of these cases, as opposed to an accuracy of 98 per cent among the first trimester cases.

Pregnant nonectopic group. Among the 123 cases of intrauterine pregnancy, 75 pregnancy tests were performed. As shown in Table IX, A, 71 were positive, 2 negative, and 2 equivocal. Of the 2 equivocal results, one might be regarded as a technical error, since it was read at 20 hours; the other was associated with an abortion 3 months later. In any event, these tests should have been repeated. The 2 negative results can hardly be regarded as errors: a previous pregnancy test had been positive in one case; the patient then aborted and the negative test was obtained after the abortion. The other test should be regarded as a technical error, for it was read at 6 hours; another test on the same patient was run simultaneously with different mice, read at the proper 24 hour interval, and interpreted as positive.

Nonpregnant nonectopic group. Pregnancy tests were performed in 120 of the 168 cases which were not associated with pregnancy in the tube or the uterus (Table IX, A). Equivocal results were obtained in 2 instances; these tests should have been repeated. There were 3 results which were probably false positives. In one case the test was read as positive after 6 hours, negative in 24 hours. There was one positive result which was undoubtedly due to a mix-up in names. A note on the chart explains that there were 3 patients on the ward with the same name. Another negative result was found in the case of a patient who had recently had 2 positive tests; a definitive diagnosis was never made in this case. Finally, there were 2 positive results in association with hematosalpinges. It is interesting to speculate on whether these latter 3 cases and perhaps even the 3 cases with "false-positive"

Table IX, A. Accuracy of the test

A. 209 ectopic 123 had no pregnancy test performed 86 had pregnancy test performed 75 positive only 9 negative only

B.	123 pr	egnant, nonectopic
	4	8 had no pregnancy test performed
	7	5 had pregnancy test performed
		71 positive only
		2 equivocal only
		O manating and maritime

2 positive and negative

	2 negative and positive
C.	168 nonpregnant, nonectopic
	48 had no pregnancy test performed
	120 had pregnancy test performed
	.110 negative only
	2 equivocal only
	4 positive and negative
	4 positive only

Table IX, B. Accuracy of the test

86 pregnancy tests amon	a the ectonic aroun
11 negative tests amon	2 with ghost villi (false negative) 3 technical errors 6 in 2nd trimester
75 pregnancy tests amon group	g the pregnant, nonectopic
2 negative tests {	1 following an abortion 1 technical error
120 pregnancy tests amo ectopic group	ng the nonpregnant, non-
8 positive tests	3 probably false positive 2 technical errors 1 without diagnosis 2 hematosalpinges

Table IX, C. Accuracy of the test

	Ectopic	Preg- nant, nonec- topic (%)	Non- preg- nant, nonec- topic (%)	Total
Crudest evalu- ation (correct results only)	87.2	94.7	91.7	91.1
Reasonable evaluation (correct re-	00.4	00.0	04.0	
sults) Possible evaluation (all but	90.4	98.6	94.8	94.5
false results)	97.4	100.0	98.2	98.5

tests might not actually have represented unrecognized ectopic pregnancies.

Of the 291 nonectopic cases, the pregnancy test alone eliminated 112 from further consideration of the diagnosis of ectopic pregnancy. Had a pregnancy test been performed in all cases it might have led to the further elimination of 47 more cases. Thus, the pregnancy test might have clarified the diagnosis in 159 or 55 per cent of these nonectopic cases.

Over-all accuracy. Table IX, B summarizes the over-all accuracy of the pregnancy tests in terms of the data presented above. Table IX, C presents an analysis of these results from three different points of view. The top line of the Table IX, C shows a total accuracy of 91 per cent; this represents the figures obtained by using all of the tests in the denominator, only the correct results in the numerator. In the second line the equivocal results and technical errors are eliminated from the denominator. In the last line all but the false-negative and the probably false-positive results are disregarded.

It would appear from these figures that the absolute accuracy of the pregnancy tests in this series exceeded 98 per cent. Although it might be argued that the useful accuracy of these tests was considerably lower, this is not necessarily true. If all equivocal tests had been repeated, all technical errors corrected, and all second trimester results ignored, this 98 per cent figure might have become a practical fact.

Comment

It would appear from this material that the diagnosis of ectopic pregnancy is seriously considered at Sloane Hospital at least twice as often as it is ultimately proved. In view of the nonspecific nature of the individual signs and symptoms of this syndrome, this seems a reasonable ratio. The average lapse of almost a week between initial investigation and final diagnosis can be similarly explained. The performance of 46 laparotomies for "ectopic pregnancies" which did not exist—even though the operation could be justified on other grounds in

13 instances—is, of course, lamentable. On the other hand, this rate of misguided operations (22 per cent) is in keeping with the (20 per cent) generally reported for this condition.

In this series the final diagnoses were reached in 67 per cent on clinical and laboratory grounds, in 23 per cent by means of minor operative procedures, and in 10 per cent by laparotomy.

There is ample evidence among these data and the diverse literature on this subject that no one sign or symptom or laboratory test is universally reliable in the recognition of ectopic pregnancies. Nor is there evidence here or elsewhere that any one minor operative procedure, such as curettage or culdoscopy, can be relied upon.

With regard to the pregnancy test, on the other hand, we believe that our data support a different sort of conclusion, namely, that—despite the fact that it is not 100 per cent accurate and despite the fact that other obstetric conditions are frequently confused with ectopic pregnancies—except in the presence of vascular collapse it is virtually mandatory that a pregnancy test be performed in every case in which an ectopic gestation is considered. With the exception of 9 "technical errors" and 10 cases in which the ectopic pregnancy was no longer viable, the 281 tests in this series were, for all practical purposes, 100 per cent accurate.

Summary

- 1. This review deals with 500 cases in which there was a presumptive diagnosis of ectopic pregnancy or "possible ectopic pregnancy" at the time of the patient's admission to the hospital.
- 2. In only 40 per cent of these cases was the diagnosis of ectopic pregnancy ultimately proved.
- 3. In 46 cases a preoperative diagnosis of ectopic pregnancy was found at laparotomy to have been in error.
- 4. Of the many diagnostic criteria used () differentiate this condition; the pregnancy test was found to be the most reliable.

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Unilateral twin tubal pregnancy

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THE first report of a unilateral twin tubal pregnancy occurred in 1891. Since then there have been a total of 81 authenticated cases. 2, 3, 4, 5, 6 The recent occurrence of two cases of this type prompted the present report.

Case reports

Case 1. This 37-year-old Negro woman, gravida iv, para ii, who had had 2 abortions, was admitted April 29, 1959, with complaints of persistent lower abdominal pain of 2 weeks' duration. The last normal menstrual period was Jan. 8, 1959. The patient bled for 2 weeks in February and spotted all month in March. There were no gastrointestinal or genitourinary complaints. Past medical and surgical histories were noncontributory. Obstetrical history revealed 2 normal deliveries 21 and 11 years before Gynecologic history revealed no pelvic inflammatory disease, regular menstrual cycles, and 2 abortions with curettage in the period between the 2 normal pregnancies. Physical examination revealed a well-developed, well-nourished patient in no distress. Blood pressure was 102/60; pulse 80; temperature 99.4° F. Positive findings were limited to the abdomen. Right lower quadrant tenderness was present but there was no rebound tenderness and no mass was palpable. The cervix was anterior, conical, and firm. There was a small amount of bleeding from the external os. The uterus was normal in size and was retroverted with some tenderness on motion. The right adnexal region contained a tender 8 to 10 cm. cystic mass close to the corpus, filling the cul-de-sac.

Laboratory findings. Sedimentation rate 18 mm. per 30 minutes; hemoglobin level 11.6 Gm. (72 per cent); white blood count, 19,200; serology findings negative; urinalysis within normal limits.

Course in hospital. Because of the persistence of the cystic mass in the right fornix and symptoms, a laparotomy was performed. Findings included filmy adhesions from uterus to the rectum. The uterus was normal in size. The left tube and ovary were adherent to the posterior leaf of broad ligament and extended into the culde-sac. The right tube was 8 cm. in length and 1.5 cm. in width except for the distal end which was dilated to 9 cm. and contained a partially extruded mass of placenta-like tissue. There was no active bleeding. The ovary was adherent to the mass. A right salpingo-oophorectomy was performed. The postoperative course was uneventful and the patient was discharged on the ninth postoperative day.

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Pathology report described a tubal rupture with a placental mass containing a vesicle filled with 10 c.c. of clear, reddish fluid, lined by a thin membrane and containing 2 embryos—0.5 cm. and 0.8 cm. in length. The ovary was fibrotic and adherent to the mass.

Case 2. This 21-year-old gravida i, para i, was admitted Aug. 8, 1958. She complained of a hypomenorrheic period in July followed by irregular vaginal bleeding and lower abdominal pain of 10 days' duration. One-half hour prior to admission there was acute lower abdominal pain which caused the patient to seek relief. There was no vertigo, fainting, or gastrointestinal or genitourinary symptoms. Past medical and surgical histories were noncontributory. Obstetrical history revealed a normal delivery in 1956. Gynecologic history revealed treatment for pelvic inflammatory disease and regular menstrual cycles. Physical examination revealed a welldeveloped, well-nourished patient in acute distress. Blood pressure was 120/70; pulse 9; temperature 99° F. Positive, physical findin s were limited to the abdomen and pelvis. The e was marked left lower quadrant tenderness and rebound, but no shifting dullness. Bimanual nce

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viginal examination revealed a closed, firm cervix exquisitely tender to motion. A tender cestic mass was palpable in the left adnexal region.

Laboratory findings. Sedimentation rate 6 mm. per 30 minutes; hemoglobin level 11.5 Gm. (70 per cent); urinalysis negative.

Course in hospital. With a tentative diagnosis of ruptured ectopic pregnancy, a cul-de-sac tap was performed and nonclotting blood was obtained. Immediate laparotomy revealed the uterus to be of normal size. The cul-de-sac was filled with old clots and fresh blood. The right tube and ovary were adherent to the posterior leaf of the broad ligament. The left tube was elongated and dilated to 3 cm. A mass of placental tissue was adherent to the left fimbriated end, near a 1 cm. perforation and to the left ovary and infundibulopelvic ligament. A left salpingo-oophorectomy was performed. The post-operative course was uneventful and the patient was discharged on the ninth postoperative day.

Pathology report described a left tube and ovary and a separate mass of placental tissue. On section of the tube, another completely intact placenta with membranes was found. The separate mass of placenta was apparently complete and separate from the intact tubal placental mass. One fetus 2 cm. in length was found among the blood clots. The ovary contained (on multiple sections) two separate and distinct corpora lutea of pregnancy. Although the second fetus was not found, the separate findings of both corpora lutea and placentas supported the diagnosis of dizygotic twin pregnancy.

Comment

During the past 28 years at Harlem Hospital there have been 1,360 tubal pregnancies. There has been a relative and absolute increase in incidence during the past 15 years when compared to the total gynecologic and obstetrical admissions to the service. With this apparent increasing incidence, attributed by some⁸⁻¹⁰ to the use of antibiotic therapy for pelvic inflammation, we may be seeing more of multiple tubal pregnancies, among which have been reported 4 cases of unilateral triplet¹¹⁻¹⁴ and one quintuplet tubal pregnancy. ¹⁵

It should be noted that, of the 81 cases previously reported, there have been only

3 cases of tubal dizygotic pregnancies. 6, 16, 17 However, according to United States vital statistics for 1946, the incidence of intrauterine dizygotic pairs occurs more frequently (65 per cent) than the monozygotic variety. The reasons for this apparent disparity can only be theorized. Factors predisposing to tubal ectopic gestation may result in the slowing of the rate of passage of the fertilized ovum through the tube. According to Stockard,18 abnormal fetal development resulting in monozygous twinning may occur at this critical time. Thus, when tubal implantation occurs and growth continues, single ovum twins result. This is in agreement with the statement made by Arey,19 who found that single ovum twins are more common in the tube than in uterine pregnancy.

Bilateral tubal pregnancy has been reported to have occurred 143 times. A review in 1957²⁰ regarded these cases as the rarest form of dizygotic pregnancies. However, the present paper reports only the fourth case in the literature of dizygotic twins of the unilateral type.

In many cases of ruptured or aborted tubal pregnancy no embryo is found. A more careful search of materials cast off into the abdominal cavity may reveal an embryo or embryos. This may aid in evaluating the true incidence of twin tubal pregnancies.

Summary

- 1. Two cases of unilateral twin tubal pregnancy have been presented, making a total of 83 cases to date.
- 2. This report includes the presentation of a case, which is the fourth in the world literature of dizygotic type of twin tubal pregnancy—the rarest form of double ovum pregnancy.
- 3. The possible mechanisms for the majority occurrence of monozygotic twins in this variety of pregnancy, has been presented.
- 4. It is recommended that blood clots from the abdomen should be part of the pathologic specimen sent to the laboratory.

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This study may reveal a second embryo and at times may be the only diagnosis of ectopic pregnancy.

We wish to thank Dr. Vera Dolgopol, Direct r of Pathology, for the examination and descritions of the pathologic specimens.

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Antenatal pulmonary embolic disease

Case report, with special reference to the therapeutic use of anticoagulants

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PULMONARY embolic complications during pregnancy are clinically rare. Since the comprehensive study by Ullery, in 1954, in which 25 cases of antenatal pulmonary embolism and infarction were surveyed from the literature, with the addition of 2 more from his own hospital records, only 16 additional cases have been reported.

One of the most effective therapeutic measures in the treatment of patients with phlebitis with or without pulmonary emboli has been the use of anticoagulants. In the pregrant woman, however, certain deterrents, the most important of which is the question of the effect of these drugs on the unborn fetus, have caused some physicians to avoid their use prenatally.

The purpose of this paper is to relate a case of pulmonary embolism occurring in the first trimester of pregnancy seen by the authors, to review all other reported cases since 1954, and to discuss the use of the anticoagulant drugs in this situation.

Case report

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A 34-year-old white gravida ii, para i, was admitted on May 23, 1958, complaining of pain across the back at the lower level of the thoracic cage. The pain had gradually increased in severity since she awoke in the morning prior to

admission to the hospital. During that evening, respirations became painful and cough developed. There was no history of hemoptysis, diaphoresis, fever, chills, leg edema, or pain.

Past history revealed that she had been examined by an internist 3 months prior to this episode, at which time some vague tenderness was elicited in the left lower quadrant of the abdomen, and a mass 3 cm. in diameter was noted in the broad ligament to the left of the fundus of the uterus.

Significant physical findings on admission were limited to the chest and abdomen. There were a few fine râles in the lower section of the right lung and a definite limitation of respiratory motion on the left side. Tenderness was again elicited in the left lower quadrant of the abdomen with deep palpation. Pulse, blood pressure, and temperature were normal. There was no evidence of any phlebitis in the lower extremities. Menses had been regular until March 21, approximately 2 months prior to admission. A pelvic examination revealed the uterus to be enlarged to about the size of an 8 weeks' pregnancy along with the presence of a walnut-sized mass in the left broad ligament.

The initial chest x-ray examination revealed an infiltrate in both lower lobes. The urine pregnancy test was positive. Other laboratory tests showed the hemoglobin content to be 11.7 Gm., hematocrit 40 per cent, leukocytes 13,000, with a moderate shift to the left and a sedimentation rate of 56 mm. per hour. The urine examination was normal.

Initial treatment was limited to bed rest, analgesics, and antibiotics. On the third hospital day, the patient had an episode of hemoptysis, and

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Table I. Cases of pulmonary thromboembolic disease

Author	No. of cases	Anti- coagulants	Deaths
Ullery ¹	20	No	17
Ullery ¹	7	Yes	0
Collins and Batson ³	3	No	3
Sibthorpe ⁴	3	No	1
Barry and Olson ⁵	1	Yes	0
Blum ⁶	2	Yes	0
Thoms ⁷	1	No	1
Wingate ⁸	1	No	1
Quenneville9	3	Yes	0
Quenneville9	. 1	No	0

the possibility of pulmonary embolus with infarction was entertained. Repeat chest films revealed some clearing on the right, but the picture of the left side showed it to be compatible with a pulmonary infarction.

The patient was placed on anticoagulant therapy employing warfarin sodium for maintenance after the prothrombin time was quickly lowered to 20 per cent with heparin. Within a few days, she complained of pain over the right chest, and x-ray studies revealed a small area of probable infarction in the right lower lobe not present on earlier films. In an attempt to ascertain the source of the emboli, and because of the previous finding of a mass in the left broad ligament, a gynecologic consultation was obtained. The examination was normal except for findings consistent with a pregnancy of approximately 12 weeks.

The patient remained in the hospital for 1 more month on anticoagulant therapy with gradual clinical improvement. The prothrombin time was maintained at about 18 per cent of normal ranging at times from 11 to 36 per cent. The dosage of warfarin sodium varied during the first 2 weeks from 5.0 to 15.0 mg. per day. After this period a maintenance dose of 7.5 mg. daily was employed with little significant fluctuation in the prothrombin times. The treatment was continued on an outpatient basis with weekly prothrombin times until the thirty-sixth week of gestation. At the time of discharge from the hospital, the chest films revealed very little change; however, over the ensuing weeks of treatment the x-ray studies showed complete clearing. The pregnancy was carried to full term, and upon the patient's admission to the hospital for delivery, the prothrombin time was again 100 per cent of normal. Delivery and puerperium were uncomplicated, and there were no discernible effects of the anticoagulant therapy in the newborn. Pelvic examination at the time of delivery failed to demonstrate any residual palpable pathology.

Review of the literature

Mansell,2 in 1952, reported a 15 per cent maternal mortality rate because of pulmonary emboli in cases of thrombophlebitis complicating pregnancy and untreated by anticoagulants or surgery. Ullery1 reported this same percentage as opposed to a 0 per cent maternal mortality rate among those patients given anticoagulants to decrease the danger of embolism. Ullery's survey of the literature revealed 126 reported cases of thrombophlebitis and phlebothrombosis in pregnant women. He found that 90 of the patients had not received anticoagulants, and of these, 18 suffered pulmonary infarctions with 15 deaths. Of the 36 women who were treated with anticoagulants, 7 had pulmonary infarctions without a single death. Ullery then reviewed 50,332 obstetric histories covering a period from 1933 to 1953 at the Philadelphia Lying-In Division of the Pennsylvania Hospital and was able to report only 9 additional cases of antepartum thrombophlebitis. Two of these patients received anticoagulant therapy and recovered without incident. Of the 7 cases not given such therapy, 2 deaths resulting from pulmonary embolism and infarction were reported.

With the case herein presented, 44 cases of antenatal pulmonary thromboembolic disease have been reported (Table I).

An analysis of Table I will reveal that 29 of these patients did not receive anti-coagulants, and that there were 23 deaths in this group. In one case⁷ among these 23 fatalities, a postmortem cesarean section was performed with the delivery of a live infant; but, in each of the other instances, the fet as was secondarily lost. Therefore, among the 29 patients with pulmonary emboli treated conservatively, there were 7 live births or a fetal salvage rate of 24 per cent. There are 13 patients who did receive anticoagular is, and with the addition of the author's case,

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a total of 14 such cases. There were 11 live births in this group or a fetal salvage rate of 78.5 per cent.

The figures in the previous paragraph seem to point to the fact that, in cases where the patient has already suffered an embolus, the anticoagulants are important and proper therapy. But, what of the pregnant patient with thrombophlebitis? What are the chances of her having an embolus? There is a wide variation of opinion, probably because of the small series of cases upon which these reports are based. They range from 20 per cent¹ to 6.3 per cent.º To date there are 89 case reports of pregnant patients suffering from thrombophlebitis who have been treated with anticoagulants. These are listed in Table II.

The most significant figures in Table II are the maternal mortality rate of 0 per cent and the 5 fetal deaths in each of which the anticoagulant drugs were believed to have had a part. Sachs and Labate¹⁴ described a patient who had received bishydroxycoumarin (Dicumarol) during the last 10 weeks of her pregnancy. The fetal heart tones disappeared 20 days prior to delivery of a marcerated fetus. Autopsy revealed a hemopericardium, massive hemorrhages into the thymus and mediastinum, and focal hemorrhages in the lungs. Blum⁶ reported a case in which fetal death occurred simultaneously with a sudden drop in the maternal prothrombin level. The patient was being treated with bishydroxycoumarin.

Autopsy examination of the stillborn fetus did not reveal any hemorrhages or other deleterious effects which might be ascribed to the therapy. Gordon and Dean¹⁰ published a case report in which a woman carrying a pregnancy was given bishydroxycoumarin because of deep femoral thrombophlebitis. At term, she was delivered of a stillborn child with grossly evident hemorrhages. The second twin died 35 days after delivery of an intracranial hemorrhage despite vitamin K therapy. Quenneville and associates9 in their series, had 3 intrauterine deaths. One could be ascribed to other causes, a second was inexplicable, and the third showed evidence of hemorrhages at the autopsy examination. Death was ascribed in the last case to the anticoagulant drug, and again in this case it was bishydroxycoumarin which was being used.

Comment

The administration of anticoagulants to the pregnant patient with thrombophlebitis has its critics and proponents. The problem is not the efficacy of these drugs in the treatment of thrombophlebitis, since this has been well established in nonpregnant patients. Rather it is a question of the effect anticoagulants may have on the fetus and whether the risk of pulmonary embolic disease and its consequences justifies their use. Meyer¹⁵ has expressed some fear of giving anticoagulants to a pregnant woman. He stated that almost certainly the prothrombin

Table II. Cases of thrombophlebitis treated with anticoagulants

Author	No. of cases	Pulmonary emboli	Maternal mortality	Fetal mortality
Ullery's survey ¹	36	7	0	1
Ullery1	2	0	0	0
Gordon and Dean ¹⁰	1	0	0	2
Bu ns11	10	0	0	0
Barry and Olson ⁵	1	1	0	0
Bl m6	3	2	0	1
Lloyd12	1	0	0	0
O' Ianesian ¹³	1	0	0	0
Quanneville and associates9	33	3	0	1
Authors	1	1	0	0
Total	89	14	0	5

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of the fetus would be affected and there might be bleeding.

Animal experimentation with the anticoagulants has supported the group which condemns their use in pregnancy. Quick16 gave bishydroxycoumarin in therapeutic dosages to pregnant dogs during the last week of gestation and found that many of the puppies were stillborn, that all of the newborn had extremely low levels of prothrombin (far below those of the mother dogs at the time of delivery), and that none of the puppies survived unless given vitamin K. Kraus and associates17 performed similar experiments using rabbits with very similar results. The clinical results reported here, however, do not seem to sustain the dire consequences demonstrated in these animal experiments.

Five fetal deaths believed to be due at least in part to the anticoagulant drugs have been reported among the 89 pregnant women treated with them. This is a significant loss,

but it is statistically much better than that reported in similar cases treated conservatively (without anticoagulants). It is noteworthy that all 5 fetal deaths occurred in patients being treated with bishydroxy-coumarin. There have been no such report with the use of heparin although approximately one fourth of the reported cases were carried on heparin. Warfarin sodium, the drug employed successfully for the case herein presented, has not been evaluated elsewhere in this regard.

Summary

- 1. A case of pulmonary embolism occurring early in pregnancy and treated with warfarin sodium for 4 months during the gestation has been presented.
- 2. The literature regarding thromboembolic pulmonary disease in pregnancy has been reviewed, and the reported cases have been tabulated and statistically analyzed.

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Antepartum pulmonary embolism

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ANTEPARTUM thrombophlebitis is a relatively rare entity, its occurrence being reported as less than 0.1 per cent. Even more rare is the associated complication of pulmonary embolism. Ullery, in a 20 year review of the literature, reports only 25 cases, while Sibthorpe has recently reported 3 more cases. The following case is presented because nowhere in the literature have we been able to find an account of fatal pulmonary embolism so early in pregnancy.

A 30-year-old white woman, gravida ii, para i, was brought to the emergency room on July 12, 1959, following a sudden syncopal attack. On admission, no pulse or blood pressure was obtainable. The patient's head and neck were cyanotic and she was extremely dyspneic and unable to talk. Although she was holding her right side, there appeared to be no abdominal guarding. An intravenous drip of plasma expander (with 4 c.c. of Levophed) was started. Type O, Rh-negative blood and positive pressure oxygen were administered and type and crossmatch obtained. Since the history was that of an early pregnancy, the possibility of a ruptured ectopic pregnancy was entertained! A posterior calpopuncture was performed but no blood or fluid was recovered. The pelvic examination ir dicated a uterus of approximately 3 months' g station. The patient failed to respond to fluids, vasopressors, and whole blood transfusion. Bood pressure and pulse were never obtainable and she was pronounced dead approximately 40 minutes after admission.

The following history was obtained from the patient's physician, after her death. She was first seen by him on June 16, 1959, because of probable pregnancy. The last normal menstrual period was April 22, 1959. She complained of dysmenorrhea as well as frequent pelvic pain and backache not related to menses. She had missed one period in February but resumed normal menses in March. She had had one pregnancy 7 years previously, resulting in the birth of a normal 8 pound male infant. The pregnancy and puerperium were uneventful. Physical examination at the first visit for the present pregnancy revealed an obese white woman (64.5 inches, 160 pounds) with tenderness in both lower quadrants of the abdomen. There was profuse leukorrhea. The cervix was slightly blue and firm but severely eroded and friable, bleeding on touch. The uterus was normal in size, shape, and position. The adnexal regions were difficult to evaluate because of exquisite tenderness.

The patient was given 2 c.c. of Ovagest to determine the presence or absence of pregnancy. A tentative diagnosis of pelvic inflammatory disease, with or without pregnancy, was entertained, and the patient was placed on antibiotic therapy.

She was next seen on June 30, 1959, with a history that she had bled scantily on June 17 and 18, but had had no bleeding since. The uterus was found to be enlarged to the size of a 2 months' gestation and the pelvic findings were otherwise normal, with the disappearance of adnexal tenderness. The expected date of confinement was considered to be Jan. 26, 1960.

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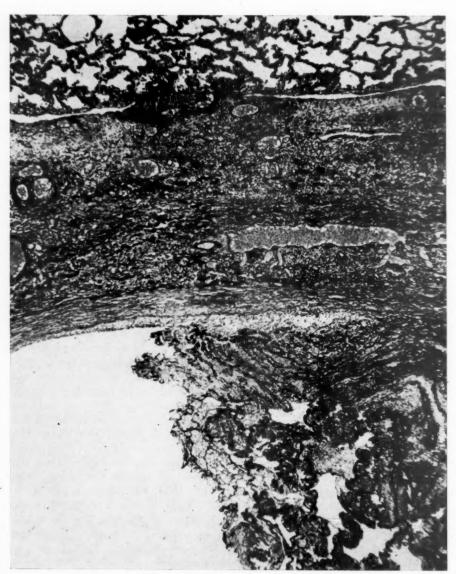


Fig. 1. Photomicrograph of lung showing the presence of a thrombus in the main pulmonary artery. (Azocarmine stain. ×160; reduced ½3.)

Pathological examination. The pathological examination was performed by the Cuyahoga County Coroner's Office and included the following findings of importance: The right lung weighed 495 grams, the left lung 475 grams. Both lungs were rubbery to palpation and cross-section revealed a dark red-purple parenchyma yielding voluminous quantities of bloody, watery fluid. The trachea and major bronchi were empty. The main pulmonary arteries and their immediate branches were filled with apparently antemortem blood clot which was adherent to

to intimal surface of the vessels. The uterus was enlarged and contained an intact pregnancy. The fetus measured 7.5 cm. from crown to heel and 6 cm. from crown to rump. The placenta was slightly detached in its inferior area. The left iliac vein and its major tributaries were occluded by antemortem thrombi.

Microscopic examination revealed most of the organs to be within normal limits except for passive congestion, most marked in the spleen and kidneys. Sections of the lung showed a considerable degree of hyperemia and pulmonary

dema. In addition, there were focal areas of telectasis. In one of the sections a laminated hrombus was noted in a major pulmonary essel (Fig. 1). This was composed of degenerting leukocytes and fibrin, and it showed an ingrowth of fibrocytes at the periphery. Sections through the left iliac vein also showed an organizing thrombus (Fig. 2). There were many fibrocytes, hemosiderophages, and an ingrowth of very small capillaries in an area near the endothelial lining. An extensive polymorphonuclear and plasmacytic reaction was noted in

the wall of a vein. Anatomic diagnosis was left ileofemoral thrombophlebitis with bilateral pulmonary embolism, pulmonary hyperemia, edema, partial atelectasis, and intrauterine pregnancy of approximately 2 to 3 months' gestation.

Comment

The occurrence of ileofemoral thromophlebitis during late pregnancy and the puerperium is well established. Predisposing factors responsible for this include obstruc-



Fig. 2. Photomicrograph of the left common iliac vein showing an organized thrombus filling the lumen. (Azocarmine stain. ×160; reduced 1/3.)

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tion to venous return with resultant stasis, changes in blood volume and viscosity and pelvic infection. Although it cannot be stated with certainty whether or not pregnancy was the major predisposing condition in this case, it appears likely that this and the pelvic infection were important factors.

The mechanism of thrombus formation in relation to its occurrence in pregnancy is clearly cited by Ullery.4 One of the primary requisites is considered to be an abnormal area of endothelium which provides a nidus for agglutination and disintegration of platelets. This results in the formation of a thrombus with a reticulum of fibrin enmeshing intact platelets. There is subsequent retraction of the primary clot followed by formation of superimposed thrombi which build up in successive layers. The final result is embolization. According to Ullery's classification of antepartum and postpartum thrombophlebitis, this case would fit into the category of silent or nonobstructing thrombophlebitis, which might more correctly be considered phlebothrombosis, in the pathologic sense. The distinction between thrombophlebitis and phlebothrombosis here, as in most cases, is of minor practical import. Inasmuch as some inflammatory changes were observed in the wall of the iliac vein, whether primary or secondary, the use of the term "thrombophlebitis" is justified.

We wish to emphasize the fact that, although extremely rare, thrombophlebitis with a resultant pulmonary embolus may occur during early pregnancy. Symptoms of the primary low-grade thrombophlebitis may be quite subtle, or absent, making the clinical diagnosis difficult, if not impossible. Diagnosis would be apparent with the onset of the classical symptoms of chest pain and dyspnea. At this point the prognosis would be extremely grave and treatment supportive and expectant. If the diagnosis can be made before the onset of the embolic episode, the vigorous use of antibiotics, with a short-acting anticoagulant, under careful supervision, would be indicated.¹

Summary and conclusions

A case of fatal pulmonary embolism in the first trimester of pregnancy is reported. While several cases of pulmonary embolism during pregnancy have been cited, none has been reported at this early stage. (Dr. Hyatt Reitman, in a report to the Cleveland Society of Obstetrics and Gynecology on maternal deaths in Cuyahoga County for 1958, reported a similar case of fatal pulmonary embolism in the first trimester of pregnancy.²) This case should emphasize the importance of careful observation of a patient who shows clinical evidence of low-grade thrombophlebitis or pelvic infection during early pregnancy.

We are indebted to Dr. Lester Adelson, Assistant Coroner of Cuyahoga County, who performed the autopsy, to Dr. Harry Goldblatt for his criticism, and to Mr. Robert Newhouse for the photomicrographs.

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Severe hypokalemia due to prolonged administration of chlorothiazide during pregnancy

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CHLOROTHIAZIDE currently is a popular diuretic used either to rid the pregnant woman of edema fluid or to prevent its accumulation. Studies have been reported in which prolonged administration of this drug during pregnancy apparently produced no adverse effects on blood electrolytes.^{1, 2} On the other hand, it is established that the continual administration of chlorothiazide to nonpregnant subjects for control of edema or hypertension can produce considerable derangement of the body composition including hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hyperuricemia, and possibly hypomagnesemia.³⁻⁵

Two cases of extensive metabolic derangement in pregnant women following prolonged administration of chlorothiazide which emphasize the potency of this drug have been encountered during a 6 month period at Parkland Memorial Hospital.

Case reports

Case 1. Y. R., a 20-year-old unmarried Negro hospital employee, was pregnant for the first time. Pregnancy was complicated by nausea and vomiting and near the end of the first trimester she was admitted to the hospital with this compaint. Extensive studies of hepatic function revaled no abnormality. The hematocrit determination

nation was 34. The nausea and vomiting subsided considerably and she was discharged 11 days after admission.

During the fifth month of gestation she was noted to have gained 16 pounds in 4 weeks, and pretibial edema was detected. She was given 6 tablets of chlorothiazide, 0.5 Gm. each, to take 2 a day for 3 days. When seen one week later she had lost 9 pounds and was described as asymptomatic except for "indigestion" and occasional vomiting. No more chlorothiazide was prescribed. During the next 6 weeks her condition remained the same. She gained no weight during this time.

When 28 weeks pregnant she came to the hospital complaining of cramping abdominal pain. Initially, the blood pressure could not be detected, the pulse was 116 per minute, and fetal heart tones were absent. The patient, however, did not appear to be seriously ill. The cervix was 6 cm. dilated and delivery was imminent. An intravenous infusion of Ringer's lactate solution was started and the blood pressure almost immediately thereafter was noted to be 100/80 mm. Hg. Urine was present in the bladder. Diagnoses of active premature labor and possibly supine hypotension of pregnancy were made. Unexplained were a hematocrit determination of 50 and moderately icteric plasma.

Spontaneous delivery promptly followed without difficulty and blood loss was minimal. The stillborn fetus was not macerated. A total of 1 L. of Ringer's lactate solution was given. Throughout the remainder of the day of delivery vital signs were normal. The patient seemed depressed presumably because of the fate of the fetus.

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Table I. Blood studies in Case 1

	Day of treatment				
	1	2	3	7	17
BUN (mg./100 ml.)	119	65	19	11	-
Cl (mEq./L.)	< 60	78	101	101	
CO ₂ (mEq./L.)	>46	43	33	23	
Na (mEq./L.)	131	141	141	136	
K (mEq./L.)	2.0	3.5	5.4	4.9	-
Uric acid (mg./100 ml.)	22.0	_	6.6	-	2.3
Plasma proteins (Gm./100 ml.)	6.4		4.8	-	
Hematocrit	48		34	_	34
Bilirubin (mg./100 ml.)	1.2	-	-	0.3	-
Serum transaminase (GOT)	184	-		_	16

The day after delivery she was anorexic but did not vomit. Skin turgor seemed reduced and she was found to weigh appreciably less than when last seen in clinic 3 weeks before. A complete urinalysis revealed an acid urine with slight proteinuria and specific gravity of 1.014. There was no ketonuria. The hematocrit determination was 48, the serum bilirubin was 1.4 mg. per 100 ml., and the serum glutamic oxalacetic transaminase activity was appreciably elevated. The blood pressure and pulse remained normal.

The following day more extensive chemical studies of the blood were carried out. As shown in Table I, severe hypokalemia, hypochloremia, alkalosis, hyperuricemia, and azotemia were found. The electrocardiographic changes of severe hypokalemia were demonstrated. The patient when directly questioned admitted that for about 6 weeks she had each day taken 2 tablets of chlorothiazide which had been obtained from another hospital employee.

One liter of isotonic saline solution containing 40 mEq. of potassium chloride was infused intravenously. Urine output during the course of this infusion was good so it was considered safe to give large amounts of potassium even though azotemia was present. Two liters of 5 per cent glucose in isotonic saline containing 160 mEq. of potassium was administered during the remainder of the day. The urinary output was 1,400 ml. As shown in Table I, this resulted in considerable correction of the blood electrolyte and associated abnormalities. The next day she received intravenously 3 L. of 5 per cent glucose in isotonic saline plus 160 mEq. of potassium and 85 mEq. of magnesium in the form of magnesium sulfate. She was offered fluids and food by mouth which she took reasonably well. The urine output equaled that of the previous day. Forty-eight hours after therapy had been started there was nearly complete correction of the electrolyte deficits and the azotemia. During this period of electrolyte replacement and hydration the hematocrit and plasma protein concentration each fell about 25 per cent to 34 and 4.8 Gm. per 100 ml., respectively.

The third day she received 1 L. of 5 per cent glucose in isotonic saline with 40 mEq. of potassium. Following this she was ingesting fluid and food in adequate amounts so intravenous therapy was discontinued.

After repair of the fluid and electrolyte deficits studies of hepatic function and a biopsy of the liver revealed no abnormalities, nor did roentgenographic examinations of the stomach, upper intestine, bile ducts, and gall bladder. Renal function as measured by phenolsulfonphthalein excretion was normal. She was asymptomatic when discharged from the hospital.

Case 2. P. M., a 19-year-old Negro patient, was sent by her physician to Parkland Memorial Hospital when about 37 weeks pregnant because of hypertension and edema. She had been noted to be hypertensive during 2 previous pregnancies which terminated in abortion. During the first trimester of the current pregnancy therapy with desiccated thyroid in a dose of 64 mg. per day had been initiated. Throughout the second and third trimesters chlorothiazide, 1 Gm. daily, was administered intermittently whenever she showed evidence of excessive weight gain. The exact amount taken during this time is unknown.

When she was 35 weeks pregnant the blood pressure was 150/100 mm. Hg. She had gained 9 pounds during the previous 2 weeks. There was roentgenographic evidence of cardiac enlargement and her physician thought there might be early cardiac failure. Digitalis, reserpine, and chlorothiazide, 1 Gm. per day, were prescribed along with a glass of orange juice each day.

hanced by hypokalemia.6 There was also

knowledge that the patient had been taking chlorothiazide for some time. It has long been known that digitalis intoxication is en-

moderate alkalosis without hyponatremia, azotemia, or dehydration.

She stated she lost 12 pounds during the first week after therapy was started. She continued to take these medications, with the exception of the orange juice, for another week prior to being admitted to the hospital.

At the time of admission the blood pressure was 170/120 mm. Hg. There was pretibial edema but no proteinuria or oliguria. The pulse rate was 80 with bigeminy. This evidence of digitalis intoxication suggested the possibility of hypokalemia. The serum potassium level the next day was found in 2 samples of serum to be less than 2.0 mEq. per liter and an electrocardiogram showed evidence of digitalis intoxication and hypokalemia. Less marked changes in other blood electrolytes were found. There was a moderate metabolic alkalosis with the serum chloride concentration 84 mEq. per liter, carbon dioxide combining power 34 mEq. per liter, and sodium 146 mEq. per liter. The blood urea nitrogen was 10 mg. per 100 ml. and the hematocrit determination was 34.

In the meantime amniotomy was performed and a dilute infusion of oxytocin was started intravenously. In spite of the marked hypokalemia effective uterine contractions resulted and the cervix changed from uneffaced and fingertip dilatation to nearly completely effaced and 3 to 4 cm. dilatation. At this time 40 mEq. of potassium chloride was given intravenously and then the oxytocin infusion was restarted.

Delivery occurred 1½ hours later and was uncomplicated. The infant weighed 2,020 grams. Resuscitation was not required. He was considered normal when subsequently discharged from the premature nursery.

The morning after delivery the serum potassium level was 2.0 mEq. per liter. Since the patient was able to take fluid and food by mouth she was placed on a regular diet plus supplementary oral potassium chloride.

She was last seen 3 months after delivery. At that time she was symptom-free. The serum potassium concentration was 4.3 mEq. per liter and the blood pressure was 140/94 mm. Hg.

Comment

Severe hypokalemia was demontrated by means of flame photometry and electrocardiography in both of these patients following the prolonged ingestion of chlorothiazide. In the second case it was suspected when the patient was admitted in early labor because of evidence of digitalis intoxication and

In the first case, however, much more extensive metabolic derangement was found. Severe azotemia must have been caused by the reduction in the volume of extracellular fluid and, in turn, a marked reduction in renal blood flow and glomerular filtration rate. Once the fluid and electrolyte deficits were corrected the azotemia promptly cleared. A few days later phenolsulfonphthalein excretion was normal, indicating that neither chronic renal disease nor recently acquired extensive tubular damage was present. That there was a severe deficit in extracellular fluid volume is also supported by the fall in hematocrit determination from 48 to 34, the drop in plasma protein concentration from 6.4 to 4.8 Gm. per 100 ml., and a weight gain during the first 10 days of the puerperium of more than 10 pounds. This deficit undoubtedly was the cause of the hypotension found when she came to the hospital.

The cause of the quite recent intrauterine death of the fetus in Case 1 is unknown. The fetus may have suffered equally intense metabolic derangement. Whether it was similarly depleted of potassium is unknown. Maternal hypotension could also have caused or at least contributed considerably to its death. In Case 2 the fetus did not succumb even though there was severe maternal hypokalemia shortly before delivery. Maternal hypotension was never noted, nor was fetal distress detected.

One of the manifestations of potassium depletion is impaired muscle function. In spite of the low serum potassium levels in these 2 women myometrial activity did not seem to be affected either during labor or immediately after delivery. In both instances following delivery the uterus contracted well and blood loss was minimal. This suggests that the myometrial activity is less susceptible to changes in potassium content or that

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the myometrium avidly holds on to potassium even when there is a marked loss from the rest of the body.

Although it has been reported by others that prolonged administration of chlorothiazide during pregnancy did not produce any significant alteration in the concentration of serum electrolytes, after the 2 experiences described above we are reluctant to adopt such an attitude at Parkland Memorial Hospital. Chesley and Uichanco⁷ and Assali and associates⁸ have shown that in pregnant edematous women chlorothiazide exerts its major effect on sodium excretion and water loss within the first 3 days. Consequently, it would seem that interrupted therapy with chlorothiazide, administering the drug for 3 days and then discontinuing for 3 to 4 days,

should serve to combat excessive fluid retention and at the same time reduce the likelihood of as dangerous a degree of hypokal emia as was encountered in these 2 patients

Summary and conclusions

In spite of the reports of others that continuous chlorothiazide therapy produced little change in serum electrolytes in pregnant women, such a practice can prove dangerous. Two cases of pregnancy with severe hypokalemia and metabolic alkalosis following the prolonged ingestion of chlorothiazide are presented.

It is recommended that therapy with this drug be limited to 3 days per week and that the amount of the drug dispensed at one time be restricted.

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Trial of thalidomide in insomnia associated with the third trimester

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As THE period of pregnancy progresses, the complaint of insomnia occurs relatively more frequently. It is difficult for some patients to sleep because of fetal movements. In other cases, insomnia results from the patient's difficulty in obtaining a comfortable position because of abdominal enlargement. As the size of the urinary bladder decreases, nocturia becomes common, and even those patients who had slept earlier in the night frequently have difficulty getting back to sleep. As the period of childbirth approaches, anxiety and apprehension often contribute to the severity of insomnia.

Insomnia occurring primarily during the third trimester of pregnancy is a frequent finding. The relatively high incidence of this complaint is indicated by the fact that in the 5 month period of study during which I delivered approximately 125 obstetric patients, I had occasion to test a new drug, thalidomide, in 81.

If a sleep-inducing agent is used in the treatment of insomnia occurring late in pregnancy, it is important that it should induce a restful slumber which is sufficiently similar to normal sleep that expectant mothers who suffer from nocturia will have no difficulty either in having to get up at night or in returning to sleep. The medication should be

fast-acting, as effective as the most active of the barbiturates, and more effective than the milder preparations that are helpful in only some patients. It should induce slumber without a preliminary period of excitement. After taking the drug, the patient should awaken in the morning refreshed and able to perform her usual household duties. The medication should not cause addiction or be habit-forming. A sleep-inducing agent should have a very wide margin of safety, primarily because of the hazard of accidental overdosage when there are children in the household but also because of the occasional patient who is dangerously depressed. Published reports indicate that a new compound, thalidomide, may fulfill the requirements listed above.

The test drug

Thalidomide is chemically the imide of phthalimido glutaric acid. The structure can be represented as follows:

Thalidomide differs from derivatives of barbituric acid and other hypnotics not only

Kevadon is the trademark of the Wm. S. Merrell Co., Division of Richardson-Merrell, Inc., Cincinnati, and Contergan is the trademark of the National Drug Co., Division of Richardson-Merrell, Inc., Philadelphia, for their brands of thalidomide.

structurally but also pharmacologically. It does not put experimental animals to sleep; therefore, a human dose cannot be predicted on the basis of pharmacology. Since the compound does not depress respiration or produce circulatory collapse, there is no danger to the baby if some of it appears in the milk or passes the placental barrier. Studies on the metabolism, fate, and tissue distribution of thalidomide are being conducted with radioactive material but the data have not been published.

Clinical reports

Jung¹ described a series of 300 patients in whom thalidomide appeared to induce restful slumber which he described as persisting "slightly longer than that produced by the barbiturates." The mean duration of sleep produced by thalidomide in a series of patients reported by Lasagna² was 7.4 hours. The same investigator³ previously had reported a mean duration of sleep of 7.4 hours for pentobarbital and 7.1 hours for secobarbital. Salter and his associates4 based their findings on reports of a total of 649 patient nights and calculated the average number of waking minutes for each patient under each of several experimental conditions. When sleep was induced by thalidomide in dosage of 100 mg., fewer waking minutes occurred than when sleep was induced by secobarbital in dosage of 200 mg.

Thalidomide has been reported to be promptly effective. Blasiu⁵ treated 370 patients with thalidomide during the postpartum period or following gynecologic procedures and concluded that the drug was effective after a period of 5 to 15 minutes. He reported that it produced no harmful effects on the nursling when given to the mother. In the Johns Hopkins study² to which reference has already been made, the onset of sleep with thalidomide occurred after an average of 23 minutes. Comparable figures for other sleep-inducing agents, studied under similar conditions and previously reported by the same investigator,3 were 36 minutes for secobarbital, 40 minutes for pentobarbital, 45 minutes for methyprylon, 51 minutes for

phenobarbital, and 66 minutes for meprobamate.

Thalidomide has been described to be a least as effective as the most potent of the barbiturates. Burley and his associates6 administered thalidomide to a group of 83 patients, 49 of whom had previously required secobarbital, pentobarbital, butabarbital, or amobarbital. Eighty-two per cent of the patients found thalidomide equal to or superior to the most satisfactory of the barbiturates. and only 59 per cent found the barbiturates previously used to be equal to or superior to thalidomide. The figures amount to more than 100 per cent because 45 per cent of the patients slept equally well on either type of medication. Salter and his associates4 concluded from their analysis of 649 patient nights that the milligram potency of thalidomide as a sleep-inducing agent was more than twice that of secobarbital.

Burley and his associates,⁶ Mandarino,⁷ and Esser and Heinzler⁸ have called specific attention to the absence of a preliminary period of excitement preceding the induction of sleep by thalidomide. Nowhere in the first twelve reports¹⁻¹² is any mention made of a preliminary period of excitement with the new drug.

Thalidomide in the effective sleep-inducing dose is described as virtually free from any tendency to produce drowsiness or vertigo the following morning. Blasiu⁵ referred specifically to an absence of side effects in his 370 obstetric and gynecologic patients treated with thalidomide, as did Esser and Heinzler⁸ and Loos,⁹ who studied a group of 141 patients hospitalized because of war injuries. In a series of 87 patients, some of whom were hospitalized, Mandarino⁷ reported only one case of morning drowsiness.

Specific reference to the absence of addiction and habit formation is made by Jung, Esser and Heinzler,⁸ Schober,¹⁰ and Gray and associates.¹¹ The confirmatory opinion of Cohen¹² is based on experience with daily doses of 2,500 mg. of thalidomide which could be given for substantial periods of time and then stopped abruptly without occurrence of withdrawal symptoms.

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The wide margin of safety characteristic of thalidomide is unique among potent sleepinducing agents. The lethal dose for experinental animals has not been calculated because all animals have survived the largest coses that it has been possible to administer either orally or by injection.13 Blood counts, urinalyses, and liver and kidney function tests have been conducted in human beings and reported by four different groups of investigators.1, 8, 11, 12 One of these investigators12 conducted his safety determinations on patients who were given thalidomide in daily dosage of 2,500 mg. No measurable impairment of the function of any of the vital organs was found.

The present study

Since thalidomide seemed to fulfill the requirements for a satisfactory sleep-inducing agent that could be used late in pregnancy, this drug was selected for trial in a group of 81 pregnant patients. These patients were originally selected for study because of the complaint of insomnia occurring late in pregnancy. However, results in this group were so satisfactory that 22 additional patients who were not pregnant but who suffered from insomnia also treated with thalidomide. Because of the similarity in response of the two groups, the therapeutic results are reported on the basis of study of a single group of 103 patients. Since most of them were pregnant, the vast majority of patients studied were in the age group of 21 to 39.

The test drug, thalidomide, was administered in one of three dosage schedules, depending somewhat upon the circumstances. If insomnia was related largely to tension and anxiety occurring during the day, the drug was given in dosage of 25 mg. three times a day and a fourth dose was given at the hour of sleep. If insomnia was due almost entirely to excessive fetal motion or to the abdominal enlargement, a single dose of 0 mg. thalidomide was usually given at the hour of sleep. The third schedule of 100 mg. halidomide given at the hour of sleep was employed in only 27 patients (5 who did not

respond favorably to single doses of 50 mg. plus 22 others who were simply tested on a double dose to find out whether or not they would be drowsy the next morning). Since some patients received more than one dosage schedule, the total of 103 patients are reported in terms of 140 patients responding to one of the three dosage schedules. The pregnant patients varied in age from 18 to 40, and the nonpregnant patients varied in age from 22 to 64. Those who were not pregnant were usually seen during the postoperative period following gynecologic operations or they were treated for anxiety and apprehension associated with the menopause.

Results

Induction of sleep with thalidomide in one of the three dosage schedules outlined above was achieved successfully in 92 of 103 patients (89.3 per cent). Freedom from morning drowsiness was reported for 101 of 103 patients (98.0 per cent). Other than the single case of drowsiness, no side effects were encountered.

Sixty of the patients were treated with thalidomide in dosage of 25 mg. four times a day. These were patients in whom insomnia was associated primarily with daytime anxiety. Satisfactory sleep was induced in 51 (85 per cent). There was no correlation between the age of the patient and the frequency of failure which was noted in 9 of the total of 60 patients. Drowsiness did not occur at this dosage level. Fifty-three of the patients were treated with 50 mg. of thalidomide at the hour of sleep. The successful induction of sleep was obtained in 48 (90.5 per cent), and only one patient (1.9 per cent) experienced drowsiness the next morning. The poorest therapeutic results were obtained in the 16 patients in the age group of 30 to 39 receiving 50 mg. of thalidomide. In this group there were 3 therapeutic failures; therefore, the percentage of patients responding was only 81.2 per cent.

Only 27 patients were tested with 100 mg. thalidomide at the hour of sleep. There were two therapeutic failures and one instance of drowsiness the next morning. Accordingly,

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the percentage responding favorably to the higher dose of thalidomide was 92.6.

The two age groups which comprised a sufficient number of patients so that some idea of relative efficacy of thalidomide in those of different ages might be suggested were those 21 to 29 years of age (50 patients) and those 30 to 39 years of age (32 patients in whom 44 dosage levels were evaluated). In the group aged 21 to 29, no drowsiness occurred and 90 per cent of the patients obtained satisfactory induction of sleep. Twenty-eight of these patients received 25 mg. of thalidomide four times daily and 22 received 50 mg. at the hour of sleep. Even though satisfactory results were obtained in 49 of these 50 patients, 8 were tested with 100 mg. None was drowsy the next morning. In the age group of 30 to 39, induction of sleep occurred in 81 per cent of the patients receiving 25 mg. thalidomide four times a day, in 81.2 per cent of those receiving 50 mg. at the hour of sleep, and in 85.6 per cent of those receiving 100 mg. at the hour of sleep. Drowsiness was experienced by only one patient who received 100 mg. thalidomide.

Just as Blasiu⁵ reported no deleterious effect on nursing infants when thalidomide was administered to the mother during the postpartum period, similarly there was no deleterious effect upon the babies delivered of mothers who had been receiving thalidomide late in pregnancy. If the compound did pass the placental barrier it did not influence respiration of the baby.

Summary and conclusion

Insomnia occurs commonly during the third trimester of pregnancy. A new sleepinducing agent, thalidomide, was tested late in pregnancy in 81 patients and in 22 nonpregnant patients also suffering from insomnia. When sleep disturbances were associated primarily with anxiety and apprehension occurring during the day, the drug was given in dosage of 25 mg. four times daily. When insomnia was due mostly to abdominal enlargement and fetal motion, the usual dose was 50 mg. at the hour of sleep; but, in those patients tested, doses of 100 mg. were almost equally well tolerated. Successful induction of sleep was attained in 89.3 per cent of the patients, and freedom from morning drowsiness was reported by 98.0 per cent of the patients. Thalidomide is a safe and effective sleep-inducing agent which seems to fulfill the requirements outlined in this paper for a satisfactory drug to be used late in pregnancy.

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Lidocaine or dibucaine for saddle block anesthesia—an analysis

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THE well-prepared study by Phillips and his group¹ on the comparative merit of dibucaine* and lidocaine† was an extremely interesting report, for it raised some very intriguing questions. Would lidocaine prove to be a superior agent for use in obstetrical saddle block anesthesia in other, perhaps less experienced, hands? Would others find that it was more reliable than dibucaine—a drug that has had years of experience and has become almost synonymous with the term "saddle block anesthesia"?

The study conducted in an effort to come to a valid answer to these questions forms the basis of this report.

Methods

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60. H.: As spinal anesthesia is used almost exclusively on this service, it was simple to alternate the two drugs at the time each spinal tray was set up in the delivery rooms, and thus decrease the possibility of a sampling error. Due to the shortage of anesthesiologists in the Air Force all spinals were, of necessity, administered by the obstetrical staff; 1 c.c. of whichever agent

was on the tray was used. All spinals were administered with the patient in the sitting position, with use of a 22 gauge needle, through the fourth interspace; after which she was kept in the sitting position for 30 seconds, timed by the clock. The patient was then placed flat on the table, with her head elevated on a pillow, and the table moved from a slight Trendelenburg position only when necessary to adjust the level of anesthesia. After the patient was placed in the supine position, the level of anesthesia was determined at half minute intervals until it failed to rise any longer or until the desired level was reached. It should be noted that a level of T-10 or T-9 was considered preferable, although not reached as often as desired because of the relative inexperience of some of the staff.

As this study was directed toward a comparison of these anesthetic agents, all anesthetic levels other than T-11, T-10, and T-9 were excluded for they were not considered to represent a fair evaluation. A remaining total of 185 patients receiving dibucaine and a like number receiving lidocaine are available for study.

Follow-up

After delivery the obstetrician filled out a special card noting the drug used, anesthetic level obtained, time required to produce the level, adequacy of anesthesia, type of discomfort the patient experienced, and what supplementation was given. In addition the blood pressure was charted prior to and after the saddle block and when the

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The contents of this article reflect the author's personal views and should in no way be construed as a statement of official Air Force policy.

*Nupercaine, Ciba Pharmaceutical Products, Inc.

†Xylocaine, Astra Pharmaceutical Products, Inc. patient left the delivery table. All hypotensive reactions were recorded, and the duration and therapy were noted. An effort was made to check the patient one-half hour and one hour after delivery, noting the blood pressure, sensory level, and motor loss, and these findings were also recorded on the card. After the patient's discharge from the hospital, the card was finalized and all complications noted, including their duration and therapy.

Results

Studies of a comparative nature must be composed of like factors in each group, except for the unit under consideration, for the results to be valid. In this one, even though bias was avoided as much as possible, certain discrepancies are evident. There were 32 per cent primiparas and 4.3 per cent spontaneous deliveries in the lidocaine group, and 39 per cent primiparas and 7.5 per cent spontaneous deliveries in the dibucaine group. Other features such as anesthetic skill, anesthetic technique, preanesthetic medication, age, color, etc., were largely the same in each group. As noted, there was but a small percentage of spontaneous deliveries in each group, the remainder being operative in nature. These consisted largely of low or outlet forceps and episiotomy, although rotations, midforceps, and manual removal of the placenta were noted in essentially equal proportions. Cesarean sections are excluded, and patients with breech presentations received another type of anesthesia.

The average time interval elapsing between administration of each agent and the production of hypesthesia at the desired level was 230.9 seconds with dibucaine and 162.9 seconds with lidocaine. In each group, it was noted that the time intervals were essentially the same regardless of the level eventually obtained. Not only, therefore, can lidocaine be expected to produce hypesthesia in less time than dibucaine, but it has another, perhaps more important, advantage. The onset of warmth and/or tingling in the patient's toes was consistently

noted within one minute after administration, thus giving her assurance of incipient relief of discomfort. Many patients stated that they could "feel it working" as they were placed in the supine position. The psychic lift this produces should not be underestimated.

In order to maintain complete fairness in this evaluation, each drug was subdivided according to the level of anesthesia obtained. In this manner all doubt that one group reached higher levels and thus produced better anesthesia could be eliminated. Reference to Table I will show the results in regard to adequacy of relief of pain, as evaluated by the obstetrician observing and listening to the patient's reactions and/or comments.

Those patients classified as having totally adequate anesthesia were those who had no discomfort during delivery. Those classified as having partially adequate relief experienced some discomfort during delivery, usually secondary to pressure on the fundus or manual removal of the placenta, which was not severe enough to make additional anesthesia or analgesia necessary. Those coded as requiring supplementation had such inadequate anesthesia that they required trichloroethylene with or without pudendal block for relief of their pain.

An effort was made to evaluate the duration of anesthesia in each group, using the

Table I

Level anesthesia	Pain relief	Lido- caine	Dibu- caine
T-11	Totally adequate	30	17
	Partially adequate	5	26
	Required supplement	0	2
T-10	Totally adequate	87	60
	Partially adequate	0	24
	Required supplement	0	6
T-9	Totally adequate	62	37
	Partially adequate	1	9
	Required supplement	0	4
Total	Totally adequate	96.8%	61.79
group	Partially adequate	3.2%	31.97
	Required supplement	0.0%	6.49

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criteria previously set forth by Phillips. Unfortunately, personnel shortages made it difficult to obtain observations more often than evaluating the patient on return to the word approximately one hour after delivery. The results from these observations gave the impression, and that is all that could be gained, that the sensory levels of patients given lidocaine more often fell to T-12 or L-1, and these patients were able to help move themselves off the stretcher more often than those given dibucaine. This impression would appear to substantiate Phillips' more accurate study wherein he found a duration of motor anesthesia of 109 minutes for lidocaine and 203 minutes for dibucaine, and a duration of sensory anesthesia of 147 minutes for lidocaine and 260 minutes for dibucaine.

All patients on this service receive tranquilizing agents as part of the analgesic regimen and are, accordingly, watched carefully for any blood pressure changes. In spite of their use hypotensive reactions were noted in only two instances with dibucaine (both at T-10 levels) and once with lidocaine (at T-9). None of these were severe, nor did they require active therapy. Other reported complications of spinal anesthesia such as paresthesias, meningismus, cardiac arrest, or total spinal, were not encountered. The only complications that were noted were spinal headaches (5 per cent) and 9 instances of anesthesia levels at T-6 and above. These cases have been excluded, as they were not pertinent to the purposes of this study. One patient was, however, notable in that she received an unusually high level with lidocaine because of an error on the part of the obstetrician in time of administration. She was promptly supported by the Trendelenburg position, bag breathing with oxygen, vasopressor agents, and she emerged in a short while without sequelae and a good baby. The short duration of anesthesia produced by this dose of lidocaine, especially when spread out over a large area, may well have contributed to the favorable outcome of this potentially catastrophic complication.

Comment

In spite of this rather small series these results are statistically significant, although they might be modified to some degree, for human bias cannot be entirely eliminated from this type of study. Further credibility is, however, given to these impressions when they are compared with the previous study by Phillips and his group. When his study is combined with this one it is seen that dibucaine can be expected to produce totally adequate anesthesia in only 48 to 62 per cent of patients, whereas lidocaine can be expected to give totally adequate results in 92 to 97 per cent. It is difficult to explain the divergence in results in these two series as far as dibucaine is concerned, especially in view of the similarity of findings with lidocaine. In addition to these rather revealing findings, it should be noted that the lidocaine group in both series did not require supplemental anesthesia, whereas this was necessary in 6 to 10 per cent of patients when dibucaine was used.

Summary

- 1. One group of 185 patients received dibucaine spinal anesthesia for delivery and is compared with a like number receiving lidocaine as to rapidity of action and degree of anesthesia obtained.
- 2. Dibucaine was noted to produce hypesthesia in an average of 230.9 seconds, and lidocaine in 162.9 seconds, regardless of the level obtained.
- 3. Lidocaine repeatedly produced a sensation of warmth and/or tingling in the toes within one minute of administration. This psychic lift that "the drug is working" cannot be underestimated.
- 4. Dibucaine produced totally adequate results in 61.7 per cent, whereas lidocaine produced the same results in 96.8 per cent.
- 5. Hypotensive reactions and other complications were infrequent in each group.
- 6. Lidocaine, by virtue of its rapid action and high degree of reliability, has replaced dibucaine as the spinal anesthetic agent of choice in our delivery rooms.

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We wish to thank the obstetrical staff, without whose help these data could not have been collected, and especially Drs. Blanchard H. Texada, Dwight N. Halpern, and Edward N. Peterson.

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Maternal and fetal effects of obstetric analgesia

Intravenous use of promethazine and meperidine

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THE continued search for an ideal agent or combination of agents to provide satisfactory obstetric analgesia without harmful maternal or fetal effect stimulated this investigation. The purpose of this study is to evaluate the maternal and fetal effects of a combination of promethazine and meperidine* administered in labor.

Meperidine has been well proved as an excellent obstetric analgesic agent.1 However, it must be used with extreme caution since large doses may cause fetal depression.2 Promethazine hydrochloride, a potent antihistamine, has many clinical applications. Chemically, promethazine hydrochloride is N-(2'-dimethylamine-2'methyl) ethyl phenothiazine hydrochloride. It has been shown to be effective in the prevention and control of nausea and vomiting,8 as well as markedly enhancing the effect of various narcotics and sedatives.4 With these properties in mind the combination of promethazine and meperidine for obstetric analgesia deserves complete evaluation.

Material

The medication used in this study consisted of a combination of promethazine and meperidine, in equal portions, 50 mg. of each per cubic centimeter, in disposable

cartridges. During the past 12 months nearly all term clinic patients have received this combination as an analgesic agent while in labor. Of this group 400 cases have been evaluated. The cases were studies at random with the only criteria being availability to carry out the evaluation. All common types of anesthesia for delivery are well represented in the study. One hundred and twenty of the patients evaluated were primigravidas.

Methods

A. Medication routine. Once good labor was established the patients were given 1 c.c. of the combination intravenously. An attempt was made to give the medication as soon as uterine contractions were regular and less than 5 minutes apart, and not delay until the patient was uncomfortable or had reached a given amount of cervical dilatation. One half the original dose was repeated every 2 hours as needed to give the desired analgesic effect. Patients who received additional medication with known analgesic or sedative effect were not considered in the study. Patients who received narcotic antagonists were also not studied.

B. Evaluation.

1. Clinical evaluation of the medications. The effect of the medication was evaluated by the house staff following the patient in labor. Each case was scored according to the following criteria:

EXCELLENT. Sleeping during and between contractions.

From the Department of Obstetrics and Gynecology, Ohio State University Health Center.

*Phenergan hydrochloride and meperidine supplied by Wyeth Laboratories.

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Table I. Amount of medication required

No. of injections per patient	No. of cases	Total dose of promethazine-meperidine (mg.)	Per cent
1	343	50-50	85.8
2	47	75-75	11.7
3	8	100-100	2.0
4	2	125-125	0.5

Table II. Physician's evaluation of medication effect

Evaluation	No. of cases	Per cent
Excellent	137	34.3
Good	206	51.5
Fair	42	10.5
Poor	15	3.7

good. Sleeping between contractions—awake with contractions but comfortable.

FAIR. Relaxed but awake between contractions—mild to moderate discomfort with contractions.

POOR. Pain with contractions—not relaxed between contractions.

2. Evaluation of infants. Sixty seconds after delivery the infant was scored by the Apgar method.5, 6 Serial oxygen saturations were determined on 25 infants in an attempt to determine any degree of respiratory depression. A single scale, alternating current oximeter with an infant-sized earpiece was used for the saturation determinations. The absolute values of the arterial oxygen saturation of the intact human ear lobe were determined by photoelectric determinations. It has been shown that the standard deviation between the photoelectric and Van Slyke determinations of arterial blood saturation is 2.9 per cent. The advantage of this method is that continuous direct readings of the arterial oxygen saturation can be taken. Readings were taken until the saturation was stabilized.

Samples of cord and maternal blood were collected simultaneously for determination of promethazine blood levels in 25 cases at time of delivery. These levels were related to the time of promethazine medication.

The infants were followed while in the hospital, and all complications were recorded.

3. Patient evaluation of medication. Each patient was interviewed on the first post-partum day and asked to evaluate the analgesic, amnesic, and sedative effect of the medication. They were asked to grade each effect as excellent, good, fair, or poor.

4. Complications. Labor, delivery, and the postpartum period were followed very closely in an attempt to detect all maternal and fetal complications.

Results

After receiving the initial dose of 1 c.c. of promethazine and meperidine intravenously, most of the patients slept between contractions and were comfortable during contractions. The desired effect of the medication was reached in approximately 15 minutes, and the effect usually lasted for 3 to 4 hours. Only 14 per cent of the patients required additional injections.

Table I shows the amount of medication required to produce satisfactory analgesia. Only the initial injection of the combination was required in 343 patients. The one injection represents only 50 mg. of meperidine used during the entire duration of labor. This is a very marked decrease in the amount of the narcotic used at our hospital. Two patients required four injections; however,

Table III. Patient evaluation of medication

Evaluation	Analgesia cases	Per cent	Amnesia cases	Per cent	Sedation cases	Per cen
Excellent	223	55.8	207	57.8	288	72.0
Good	126	31.5	111	27.7	93	23.3
Fair	36	9.0	73	18.3	14	3.5
Poor	15	3.7	9	2.2	5	1.2

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they had dystocia and prolonged labor. There was no evidence of infant depression at the time of birth in these cases.

Those patients who required additional medication responded to 25 mg. of promethazine and meperidine with a similar response as they had with the original larger dose. It therefore does not appear necessary to repeat the original dose of 50 mg. of each when additional medication is needed.

Approximately 86 per cent of the patients were graded by the physician following labor as having either excellent or good effect from the medication. In general the patients were peaceful and cooperative. The results of the physician's evaluation of the effect of the medication are shown in Table II. Most of the patients could be easily aroused from their sleep and were mentally clear. This was particularly important for patients desiring to be awake with conduction anesthesia for delivery. This was also found by Weiss and McGee.⁸

Over 87 per cent of the mothers felt the medication was either excellent or good in the relief of the labor pain. Ninety-five per cent felt the sedative effect of the combination was either excellent or good with 72 per cent grading it as excellent. In general the scores from the mothers' evaluation ran higher than the physicians' clinical evaluation. In no case was the reverse true. Table III shows the maternal evaluation.

Amnesia was considered excellent if nothing other than the presence of the physician and nurse was remembered. In those who could remember labor contractions amnesia was considered poor or fair. All multiparous patients felt this combination was superior to the obstetric analgesic agents that they had received in previous labors.

One minute after delivery the infants were scored by the Apgar method. Ten or 2.5 per cent of the infants had scores of less than 6. Most of the infants, 86 per cent, acceived scores of either 9 or 10. The Apgar scores are shown on Table IV. There were no indications that the combination of promethazine and meperidine had any depressing effect on the infant. The infants with

Table IV. Apgar scores

Score	No. of cases	
10	197	
9	136	
8	33	
7	15	
6	9	
5	4	
5 4 3 2	4 3 3	
3	3	
2	0	
1	0	
0	0	
Total	400	

Table V. Complications in infants

Icteric at 24 hours	3
Umbilical hernia	1
Bilateral hydrocele	2
Cleft palate, cleft lip	3
Erythroblastosis	1
Mongoloid	1
Extra digits	3
Cord hemorrhage	- 1
Facial palsy	1
Blood in stool, undetermined cause	1
Hematoma of left adrenal	1

low Apgar scores are discussed in the portion of this paper concerning complications.

There was no increased incidence of jaundice or bleeding tendency in the newborn infants. Since many of the infants were discharged from the hospital at 72 hours of age, questionnaires were mailed to the mothers. The replies from the mothers indicated no late complications in the infants. There were no deaths in the 400 cases evaluated. Table V lists the complications in the infants.

Table VI shows that there were no unusual complications of labor and delivery which could be attributed to the previously administrated analgesia agent.

Fifteen infants required some type of resuscitation (Table VII). Ten of these had an Apgar rating of below 6, 8 of which had fetal depression prior to delivery. All 8 of these had associated complications of labor which would account for the depression. Six infants were only mildly depressed and responded to tactile stimulation. They are men-

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Table VI. Complications of labor and delivery

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Cord around infant's neck 1, 2, and 3 times, knots in cord and short cord	57
Ruptured umbilical cord	1
Partial abruptio placenta	4
Marginal placenta previa	3
Prolapsed cord	1
Difficult forcep rotations	1
Precipitous labors	5
Fetal depression prior to delivery	9

Table VII. Infants requiring resuscitation

Infant mildly depressed; responded to free oxygen and tactile stimulation	(
Fetal distress prior to delivery; persistent posterior, responded to free oxygen and tactile stimulation	
Prolapsed cord; required positive pressure oxygen	
Fetal distress prior to delivery; cord around neck 3 times; required positive pressure oxygen	
Mild depression; cord around the neck 1 or 2 times; responded to tactile stimulation	
Fetal distress 15 minutes prior to delivery; hematoma of left adrenal; required positive	
pressure resuscitation	
Difficult delivery due to shoulder dystocia; required free oxygen and tactile stimulation	
Fetal depression; required positive pressure resuscitation; no associated complication	

Table VIII. Types of anesthesia used

Anesthesia	No.	of	cases
Nitrous oxide, oxygen, and ether		106	5
Natrous oxide, oxygen, and ether			
with local		42	
Saddle block		113	3
Caudal		27	7
Pudendal		14	1
Nitrous oxide		44	
Cyclopropane		34	+
Pentothal		2	
None		17	7
Ether		1	

Table IX. Maternal side effects

Elevation of the blood pressure to		
hypertensive levels	46	(11.5%)
Hyperreactive	25	(6.0%)
Nausea and vomiting	3	,
Grand mal seizure	1	

tioned only for completeness. One infant wa depressed and required positive pressure resuscitation; there was no associated complication to account for the depression. The combination of promethazine and meperidinwas listed as the causative factor in this case.

Anesthesia was not considered as a cause of fetal depression in the study.

Table VIII shows the various types of anesthesia used in the 400 cases. Seventeen patients received no anesthesia. Most of these were multiparous patients who were comfortable during spontaneous delivery. Two of the 17 patients had forceps rotations without discomfort with only the promethazine-meperidine combination.

Fig. 1 shows the results of arterial oxygen saturation determinations in 25 infants during the first 30 minutes of life. The normal curve is taken from work done by Shields and Taylor. Twenty of the 25 determinations fell into a narrow range shown in Fig. 1. This range ran slightly higher than the curve found in the study by Shields and Taylor. In one infant (B) the arterial saturation curve ran below the normal curve after 4 minutes. This case represents the lowest determination in the series. Readings were taken at 2 minutes after birth with serial readings until 30 minutes after birth.

There is some indication from this study that the promethazine may have a stimulating effect on infant respiration. Shelton¹⁰ has also noted that those infants whose mothers received promethazine while in labor have a faster rate of oxygen saturation than those who did not have promethazine.

These levels also ran higher than those found in cases where blood was drawn and determined by the Van Slyke method. It should be pointed out, however, that these samples were frequently obtained by hee puncture. It would appear that pure arterial blood will be difficult to obtain by this technique.

Umbilical cord and maternal blood was drawn at the time of delivery in 25 cases. Fig. 2 shows the promethazine blood levels 7a

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injection of the combination. Levels were determined in the cord blood in 24 of the 25 cases and in the maternal blood in 23 of 25 cases. The presence of blood levels of promethazine at 3 and 4 hours correlates with our clinical impression that medication given intravenously has an analgesic effect for a duration of 3 to 4 hours. The data shown in Fig. 2 indicates that promethazine crosses into the fetal circulation.

The blood pressure was recorded immediately after injection of the combination, and 11.5 per cent of the patients showed pressures elevated to hypertensive levels. (Table IX shows the maternal side effects of the medication.) The pressure elevations all returned to normal levels within approximately 20 minutes. There were no ill effects seen from this transient hypertension. The inci-

dence of hypertension appears to increase when the injection is given rapidly. It is suggested that the injection be given over a 2 minute period and that the medication be repeatedly diluted by aspirating blood frequently. Six per cent of the patients were hyperreactive following intravenous injection of the combination. Postpartum interviews revealed that these patients were completely amnesic. These patients were difficult to manage and did not improve with additional medication. One patient had a grand mal seizure following the injection. Postpartum neurological evaluation and an electroencephalogram revealed that the patient had epilepsy.

Summary

1. A combination of promethazine and meperidine, 50 mg. of each per cubic centi-

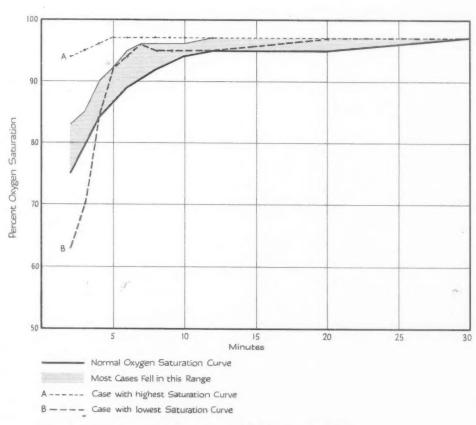


Fig. 1. Oxygen saturation curve during first 30 minutes of life.

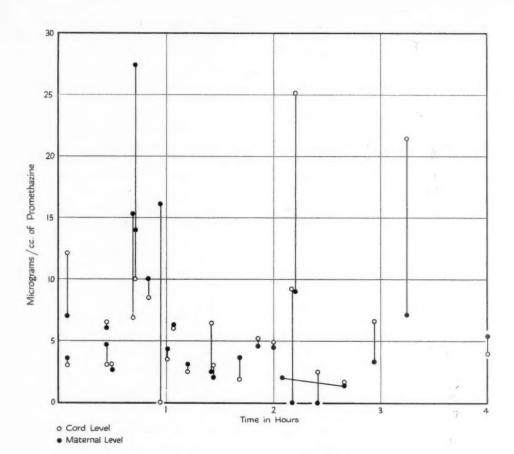


Fig. 2. Maternal and fetal blood levels of promethazine (collected simultaneously in 25 cases).

meter, was given intravenously to 400 patients as an obstetric analgesic agent.

2. Only the initial injection of promethazine and meperidine, 50 mg. of each, was required to produce satisfactory analysis in 85 per cent (343) of the patients.

3. The attending physician considered 86 per cent of the patients to have either excellent or good analgesic effect from the medication.

4. More than 87 per cent of the mothers considered the analgesic effect as excellent or good. Ninety-five per cent considered the sedative effect as excellent or good and 79.5 per cent felt they experienced an amnesic effect.

5. The newborn infant was evaluated by the Apgar method and serial arterial oxygen saturations. There was no evidence of depression of the infant due to the promethazine and meperidine.

6. Promethazine blood levels were determined in both maternal and fetal blood in 25 cases. Fetal and maternal levels are shown for a duration of at least 4 hours.

7. Transient hypertension developed in 11.5 per cent of the patients and 6 per cent were hyperreactive after receiving the injection.

Conclusion

The combination of promethazine and meperidine as an obstetric analgesic agent proved to be very satisfactory to both the physician and the patient. The amount of narcotic used for obstetric analgesia had been markedly decreased and no harmful maternal or fetal effects are produced.

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The effect of analgesia and anesthesia on the initial fetal respirations

With particular reference to the use of chloroform, levallorphan,* and halothanet

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IN JANUARY, 1847, Sir James Young Simpson¹ was the first person to use a pharmacologic agent for the relief of pain in obstetrics. After 10 months of using ether he switched to chloroform and again receives the credit for being the first to use this agent in obstetrics.

Since the early days of Simpson, Snow,² and Channing,³ many important advances and improvements have been made in the field of obstetric analgesia and anesthesia. Many analgesics, both natural and synthetic, have been used and abused in innumerable combinations. Development of new anesthetics, instruments, and techniques has done much to lower the mortality and morbidity that may accompany the injudicious use of these agents.

Verbal battles have been waged for years, and will doubtless continue far on into the future, over which agent or agents are the safest and most effective for both mother and fetus. Although the popular press emphasizes and dramatizes the possible harmful effects of analgesic and anesthetic agents, the majority

of women require, and indeed deserve, some form of pain relief during labor and parturition. the

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The mechanism of origin of respirations at birth has long been a matter of dispute. Snyder and Rosenfeld4-7 directly observed intrauterine respiratory movements in animals during a considerable portion of intrauterine life. Respiratory movements are dependent on the integrity of motor nerve cells within the respiratory center. These cells possess an intrinsic automatic rhythm controlled chemically. These specialized cells may also be influenced and modified by the chemical composition of the circulating blood, the rate of cerebral blood flow, and central nervous system depressing agents. Snyder⁷ states that extrauterine respirations are a continuation of normal intrauterine respiration and, unless the fetus' central nervous system has been depressed prior to birth, he will breathe and cry within the first 10 seconds or so of birth.

Clement Smith,⁸ on the other hand, disagrees with Snyder and claims that fetal respirations are initiated by either sensory or chemical stimuli. Under normal circumstances breathing begins as a reflex response to the sensory stimuli of exposure following birth. In infants subjected to excessive anethesia or analgesia or unresponsive to senso y impulses for other reasons, another mechanism operates: chemical changes, either anoxia, carbon dioxide excess, or a combination.

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*Lorfan tartrate (l-3-hydroxy-Nallylmorphinan tartrate), Roche Laboratories, Nutley, New Jersey.

†Fluothane (2-bromo-2-chloro-1:1:1-trifluoroethane), Ayerst Laboratories, New York 16, New York.

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tion of both, appear to initiate respirations in these cases. Smith's views are generally accepted by respiratory physiologists today.

Immaturity of the respiratory center is probably rarely, if ever, responsible for failure of the newborn infant to breathe. The stage of development of the lungs is an extremely important factor and usually after the twenty-eighth week the alveoli are sufficiently developed to provide adequate oxygenation of the blood.

The initial respiration of the normal newborn infant probably requires an intrathoracic negative pressure four to eight times as great as that needed for maintenance of respirations later. After closure of the umbilical vessels there is a sudden increase in the pulmonary artery pressure which must be rapidly followed by expansion of the pulmonary vascular bed and opening of the alveoli, or else transudation of fluid into the alveoli occurs.

Hypoxia is a necessary factor in fetal life and appears to aid in the initiation of respirations at birth. Intrauterine hypoxia, or hypoxemia as it is sometimes called, is occasionally severe enough to lead to fetal death. Some infants who suffer repeated bouts of hypoxia prior to birth are often unable to make the necessary neonatal adjustments for survival. The pathologic changes due to anoxia are congestion, edema, hemorrhage, and tissue degeneration.

Monaldi¹⁰ feels that the most important cause of neonatal apnea is a low degree of excitability of the fetus' bulbar centers which commence their activity only when stimulated by oxygen deprivation and carbon dioxide accumulation. When the oxygen concentration falls beyond certain minimal levels the reverse effect occurs and the respiratory center is depressed. Increasing the concentration of oxygen has little or no effect on fetal respirations. On the other hand, a certain minimum level of carbon dioxide is necessary for maintenance of fetal respirations.

Normal term fetal arterial oxygen saturation (umbilical vein blood) is only 50 to 60 per cent during intrauterine life. During uterine contractions there is further interference with placental function resulting in further fetal hypoxia. It appears that appea neonatorum is simply a more extensive example of the respiratory center being subjected to fetal hypoxia.

Material

This work is divided into three series. The patients were from two hospitals, the Sisters of Charity Hospital, a private hospital with predominantly white patients, and the E. J. Meyer Memorial Hospital, a large county institution with approximately a 90 per cent Negro population on the obstetric service.

After the first group had been studied, two new drugs were introduced. First, the addition of levallorphan in conjunction with narcotic sedation was instituted in an attempt to counteract the respiratory depressant effects of the narcotic analgesics. In the great majority of cases sedation consisted of alphaprodine hydrochloride* or meperidine hydrochloride.† The usual dose of alphaprodine was 40 mg. when general anesthesia was contemplated and 60 mg. when conduction or local anesthesia was anticipated. Meperidine was administered in doses of 75 to 100 mg. Scopolamine or atropine was given either with the narcotics or shortly before delivery. Secobarbital[†] was given in a great many cases early in labor, usually in doses of 180 mg. In cases in which only barbiturates were used, levallorphan was not, since it specifically inhibits narcotic-induced respiratory depression. Second, halothane anesthesia was gradually introduced in the county hospital and at present writing is being used in about 30 per cent of the deliveries.

As a result, we have three series. The first consists of 1,319 deliveries in which various anesthetics were used, the predominant one being chloroform. The second series consists of 394 consecutive deliveries in which levallorphan was used in conjunction with narcotic sedation and chloroform anesthesia. The

^{*}Nisentil hydrochloride, Roche Laboratories, Nutley, New Jersey.

[†]Demerol, Winthrop Laboratories, Inc., New York 18, New York.

[‡]Seconal, Eli Lilly & Company, Indianapolis 6, Indiana.

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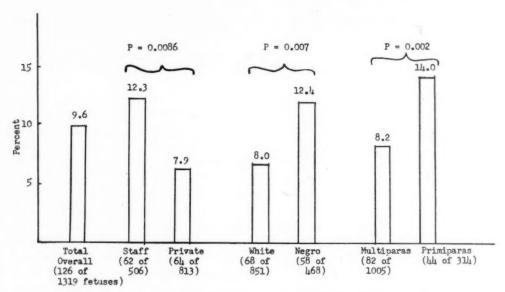


Fig. 1. Relationship of apnea neonatorum to class of patient, race, and parity, expressed in per cent.

third and smallest series represents the recent use of halothane anesthesia in 321 deliveries.

It is well known that infants born to mothers who have received neither anesthesia nor analgesia are seldom depressed, whereas those whose mothers have been sedated often begin life in an apneic state.

It is the purpose of this paper to examine some of the factors which lead to the production of apnea neonatorum.

It is at once clearly evident that there are many variables which influence the results of any approach to this study. No attempt was made to classify the degree of apnea as described by Flagg¹¹ or Lund.¹² The term "asphyxia" is not used since it is felt that this implies a severe degree of anoxia without allowing for those milder degrees of depression which prevent the fetus from breathing and crying within the first few seconds after birth.

The term "apnea neonatorum" as used in our series connotes the failure of the delivered infant to breathe within the first minute after birth. Within this 60 seconds some mucus is expressed from the nasopharynx of the infant, the cord tied and cut, the back of the infant rubbed with the fingers or a few gentle short slaps glanced off the buttocks. If the baby does not breathe within this time he is at once

taken to the resuscitator. Flagg's¹¹ resuscitator is used almost exclusively. This allows endotracheal intubation with oxygen under low pressure following gentle nasopharyngeal suction.

Results

In the first group (Fig. 1) it is seen that there is a greater incidence of apnea neonatorum in staff and Negro and primiparous patients. Statistical analysis of the three groups in Fig. 1, namely, staff versus private, white versus Negro, and primiparous versus multiparous, and application of the t test result in P values of 0.0086, 0.007, and 0.002, respectively. These are all statistically significant at the 1 per cent level of significance.

Fig. 2 shows the neonatal mortality in the various weight groups of the fetuses that required active resuscitation. One death in the mature group was due to congenital anomalies; the other was unexplained. The gross fetal mortality in the mature and premature groups totals 4 per cent, which is even better than our over-all gross fetal mortality of 6.6 per cent. Evidently the fact that a fetus requires resuscitation initially does not affect his chances for survival.

Table I correlates the anesthetic-analgesic

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combinations with fetal respirations at birth. Both the gross results and corrected figures are given. Corrections are made for immaturity, anomalies, or complications which later led to death or were obvious causes of apnea.

For instance, in the group which had neither analgesia nor anesthesia 4 fetuses did not breathe spontaneously. One, in breech presentation, was born to a primipara whose precipitate delivery began in the Admissions Department, with difficulty in extraction of the head; another had multiple anomalies incompatible with life; another was in face presentation with prolapsed cord; the fourth was born of a diabetic mother and had the umbilical cord wound tightly around its neck.

The most significant results appear in the groups with chloroform anesthesia. The uncorrected percentage of apneic fetuses was 5.7 when no narcotic analgesia was used. It rose sharply to 15.2 when chloroform was superimposed on the analgesia.

Similarly the groups in which pudendal block or conduction anesthesia was used and in which narcotics were not given during labor did not produce a single depressed fetus. When analgesia was added there was a 6.7 and 5.8 per cent incidence of apnea neonatorum, respectively (uncorrected).

Cyclopropane was used in very few cases and cannot be fairly evaluated. Ether, either open drop or more commonly in association with nitrous oxide and oxygen, was not used frequently. Probably because of the relative lack of experience with this anesthetic, the incidence of fetal depression is increased beyond what it should be.

Statistical analysis was applied to the groups of cases in which chloroform and chloroform and analgesia were used. P. <0.0001, which is highly significant at the 1 per cent level. (The figures subjected to analysis were the gross results rather than corrected figures which naturally depend on the examiner's own criteria.)

The presentation and mode of delivery as given in Table II are also shown to affect the incidence of apnea neonatorum. At one end of the scale we have 8.9 per cent apnea with occipitoanterior positions, and at the other extreme a 20 per cent rate of apnea at cesarean section.

Levallorphan was introduced in an attempt to reduce the high incidence of apnea neonatorum. In 394 consecutive live births for which chloroform anesthesia was used after narcotic analgesia and levallorphan, we clearly see that the latter is quite successful in reducing the incidence of apnea to essentially the same rate as that with chloroform alone. This is an obvious advantage to the fetus and it is now being used almost routinely in both hospitals. The results are given in Table III.

Application of the t test to the second and

Table I. Analgesia, anesthesia, and incidence of apnea neonatorum

	No. of	Gr	oss	Corr	ected
	fetuses	Apneic	%	Apneic	%
No anesthesia nor analgesia	59	4	6.8	0	0
No anesthesia; some analgesia	23	3	13.0	2	8.7
Pudendal or local without analgesia	35	0	0	0	0
Pudendal or local with analgesia	45	3	6.7	2	4.4
Conduction anesthesia; no analgesia	46	0	0	0	0
Conduction anesthesia and analgesia	69	4	5.8	2	2.5
Chloroform alone	526	30	5.7	23	4.
Chloroform and analgesia	488	74	15.2	70	14.
Ether or nitrous oxide-oxygen-ether alone	11	2	18.2	1	9.
Ether or nitrous oxide-oxygen-ether and analgesia	12	3	25.0	2	16.
Cyclopropane	3	2	67	2	67
Cyclopropane and pentothal (cesarean section)	1	1	100	1	100
Trilene	1	0	0	. 0	0

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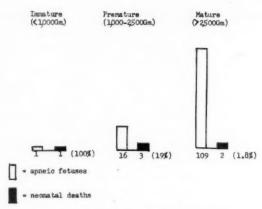


Fig. 2. Neonatal mortality in apneic fetuses.

third groups in Table III results in a P value <0.0001, which again is highly significant. This has the same significance as the analysis of the first and second groups of Table III.

The last group involves the staff patients at the county hospital who received halothane anesthesia. The advantages claimed for halothane over chloroform are less hepatotoxic and cardioexcitatory effect and a very slight incidence of postanesthetic emesis.

The effect of halothane on initial fetal respirations is noted in Table IV. There is an insignificant difference between the depressive effect of halothane and chloroform. Since work with halothane is still recent, however, we must await a longer clinical trial which will possibly result in refinements of technique and lessening of the amount of anesthetic used.

Miscellaneous factors

Labors prolonged beyond 24 hours and excessively rapid labors were also found to be attended by an increased incidence of apnea neonatorum. Prolongation of the second stage beyond an hour also increased this incidence. Deliveries performed without episiotomies produced a higher incidence of apnea, as did abruptio placentae, cord around the neck, diabetes, in the mother, and erythroblastosis fetalis.

Darke¹³ concluded that severely asphyxiated and apneic newborn infants are significantly retarded in mental development. On

the other hand, Usdin¹⁴ showed there was no difference in the I.Q.'s of 13- and 14-year-old children who had been apneic 3 minutes or longer and those of a control group born the same year. Apgar¹⁵ demonstrated in a 4 year follow-up that there was no significant correlation between oxygen saturation at birth and later intelligence.

The fetal respiratory system is particularly sensitive to narcosis. Respiratory movements may be abolished in the fetus at a level of analgesia which does not impair maternal respirations. Shields and Taylor¹⁶ demonstrated that complications of pregnancy—for example, placental disease, prolonged labor, toxemia, and major operative procedures—cause a profound depression of fetal respiratory activity.

Table II. Relationship of apnea neonatorum to presentation and delivery

Position	No,	Apneic	%
Cephalic (anterior)	1,210	108	8.9
Cephalic (posterior)	43	6	14.0
Breech	51	9	17.6
Cesarean section	15	3	20.0

Table III. Effect of levallorphan on degree of apnea neonatorum when used with chloroform

		2	
Anesthetic	No.	Apneic	%
Chloroform alone	526	30	5.7
Chloroform plus analgesia	488	74	15.2
Chloroform plus analgesia and levallorphan	394	28	7.1

Table IV. Degree of apnea produced with chloroform and halothane

Anesthetic	No.	Apneic	%
Chloroform (combined)	. 4		
from Table III	1,408	132	9.4
Halothane (with or			
without analgesia)	321	31	10.3
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Cesarean section results in depression of the fetal blood oxygen level but this is not gnificant clinically unless other serious handicaps to fetal respiratory physiology are present.

Comment

The usual better general physical condition of private and white patients and the increased incidence of anemia, toxemia, and prematurity in Negro and staff patients undoubtedly affects the incidence of apnea neonatorum as shown in Fig. 1.

The longer labors, more frequent use of analgesics, resistance of tissue, and increased incidence of toxemia in primiparas exert their influence on the incidence of apnea which is also seen in Fig. 1.

The introduction of levallorphan was demonstrated to be very effective in decreasing the number of depressed babies.

Follow-up studies on the intelligence quotients of initially apneic babies are at variance13-15 as to the final results. Nevertheless, prophylaxis in this respect is far more satisfying than treatment or correction, and it behooves the obstetrician to make every attempt to deliver active, breathing, crying, pink infants.

Conclusions

- 1. An attempt has been made to evaluate some of the variables which influence the initiation of fetal respirations.
- 2. There is a definite increase in the incidence of apnea neonatorum in infants whose mothers receive both analgesia and general anesthesia.
- 3. The incidence of apnea neonatorum can be reduced by the use of conduction or local anesthesia and the use of levallorphan with the narcotic analgesics.

I wish to acknowledge the helpful suggestions of the late Dr. Edward G. Winkler, Professor of Obstetrics and Gynecology, University of Buffalo School of Medicine, and Head of the Department of Obstetrics and Gynecology, Edward J. Meyer Memorial Hospital.

Many thanks are due Mr. J. E. Dowd of The Roswell Park Memorial Institute, Department of Statistics and Epidemiology, for his time and consideration in preparing the statistical analyses.

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CURRENT OPINION

Clinical problems

Management of eclampsia

Case presentation

This 16-year-old gravida i, para 0, white woman, with estimated date of confinement April 20, 1960, was admitted to the hospital at 1:05 p.m., March 10, 1960, in deep coma and in an extremely irritable condition. One hour prior to admission she had two convulsions. She was extremely edematous; her eyes were practically closed and there was marked pitting edema of the lower extremities and hands. The blood pressure varied between 190 to 200 systolic and 80 to 100 diastolic. On catheterization 180 c.c. of urine was obtained from the bladder. The specific gravity was 1.020; there were 4-plus albumin and occasional hyaline casts. The nonprotein nitrogen level was 41 mg. per cent. A Foley catheter was left in place and the patient's hourly urinary output for the next 4 hours varied between 10 and 15 c.c.

By 5:30 p.m., approximately 4½ hours after admission, the patient's condition appeared to be deteriorating. She was very restless, irrational, and continued to have twitching of the face and hands with increased tension of the body despite the fact that she had been given ½ grain morphine, two intramuscular injections of 2 c.c. of 50 per cent magnesium sulfate, 1,000 c.c. of 10 per cent glucose intravenously and ½ c.c. of cryptenamine (Unitensen) at 1:30 and at 3:30 p.m.

By 5:30 P.M. intravenous chlorothiazide (Diuril) was started (500 mg.) and during

the next 2 hours the patient passed 135 c.c. of urine. By repeating the intravenous chlorothiazide periodically approximately every 6 hours the patient's urinary output was maintained at an average of about 125 c.c. per hour. The urinary output reached a peak between 9:30 and 10:30 p.m. the day of admission during which time she passed 330 c.c. of urine. If the intravenous chlorothiazide was not given, the urinary output would drop below 50 c.c per hour.

The blood chemistry values are shown in Table I.

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The patient was continued on 2 c.c. of 50 per cent magnesium sulfate every 6 hours during most of the 2 weeks prior to the time of delivery and was given amobarbital sodium (sodium Amytal), 3¾ grains, intramuscularly periodically for restlessness. The patient's fluid intake was maintained at approximately 1,000 c.c. per day less than her output in order to induce weight loss.

The patient was not weighed until about the fourth day after admission at which time her weight was found to be 187 pounds. Her estimated weight at the time of admission was about 193 pounds as she had been dehydrated considerably by the time that she was weighed on the fourth day of hospitalization. Her weight reached a low point (ante partum) about 24 hours

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Date	Chlo- rides (mEq./ L)	Na (mEq./ L)	K (mEq./ L)	CO ₂ (mEq./ L)	Ca (mg.)	P (mg.)	NPN	Total protein (Gm. %)	Albu- min (Gm. %)	Globu- lin (Gm. %)	Micro- hemato- crit
March 11, 1960 (18 hrs. after admis-											
sion)	102	125	3.8				40				
March 12,											
1960	98	135	4.2					4.6	2.8	1.8	
March 13,	01	104	4.4	4.4							
1960	91	124	4.4	14							36
March 14, 1960					8	7					
March 15,											
1960	102	152	4.8	18			36				
March 17,											
1960	104	139	5.0	22							

prior to delivery at which time she weighed 169 pounds.

The blood pressure remained 190 to 200 systolic and 80 to 100 diastolic for several days. The patient's urinary output ante partum varied between about 1,275 c.c. and 4,975 c.c. and 4,575 on March 17. During the diuretic phase of this patient's eclamptic state the urine continued to show 2-plus albumin with a specific gravity of 1,004 to 1,010.

It was thought that the severe acidosis which was manifested by the carbon dioxide combining power of 14 mEq. per liter on March 13, 1960, was probably due to starvation as the patient's fluid intake had been restricted and the amount of carbohydrates consumed was apparently inadequate to prevent acidosis. At the beginning of the diuretic phase the patient was started on oral potassium chloride to prevent a hypokalemia and as is apparent from the record the serum sodium, chlorides, and potassium were maintained within normal limits. The patient legan to develop some symptoms of bladder irritation presumably due to the retention catheter having been in place for several days so the Foley catheter was removed and the patient was started on antibiotics to control the urinary infection. A medical consultant was called in to review the management.

The patient had periodic episodes of

uterine contractions during the 14 days after admission. On the twelfth day after the admission an attempt was made to induce labor by stripping the membranes and giving the patient an enema but this was unsuccessful. However, as the patient's pregnancy progressed and she became dehydrated to the maximum point, it was more difficult to control her blood pressure with hydralazine (Apresoline), cryptenamine, magnesium sulfate, and sedation. On the fifteenth hospital day with the cervix approximately 75 per cent effaced and 2 cm. dilated, and with the membranes bulging through the external cervical os, the membranes were ruptured. Labor was rapid and the patient was delivered spontaneously of a living normal 4 pound, 2 ounce, male infant.

The antihypertensive medication was continued for 48 hours post partum, at which time all medication was discontinued. The patient's blood pressure gradually dropped to 142/90 the day of discharge. The mother and the infant left the hospital in good condition.

The management of this patient differed from the usual procedure employed by us of cesarean section within 72 hours after the first convulsion because of the length of gestation (33 weeks) and because of a rapid and sustained improvement during the 2 weeks after initial hospitalization.

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Problem: The referring obstetrician requests that you discuss the management employed in this particular patient and also that you discuss the management of eclampsia in general.

Consultation

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The Bowman Gray School of Medicine

The clinical management of the eclamptic patient has plagued physicians from the beginning of medicine and midwifery. Reference to convulsive states developing in association with pregnancy are to be found in the writings of Hippocrates and Galen. The basic concepts concerning the pathogenesis of "toxemia" and even appropriate diagnostic nomenclature have been at variance as recently as the present quarter century. Eclampsia has been variously considered as a primary disease of the liver, the kidneys, and even of the breasts, the latter concept leading to therapeutic mastectomy because of a fancied resemblance of eclampsia to parturiant paresis of cattle. With the development of reasonably accurate and practical techniques of blood pressure measurement, eclampsia became recognized as primarily a vascular disease and the concept of pre-eclampsia became established.

The philosophy of treatment of eclampsia has differed widely over the years from radicalism to conservatism, from accouchement forcé as primary therapy to more restrained techniques representing variations of the now classic Stroganoff regimen. More recently, attention and clinical trial has been directed at antihypertensive drugs in the management of the essential vascular problem. Between the various divergent schools of thought have developed routines that have represented composite thinking from both the conservative and radical clinical elements and, from this background of ancient and modern clinical experience, a number of basic principles have emerged.

Noteworthy among these principles is the necessity of preventing convulsions. The means by which this is accomplished varie from clinic to clinic but at the North Carolina Baptist Hospital the use of barbiturates and morphine in adequate dosage are the mainstay of therapy. Intravenous amobarbital sodium is used to control the immediate convulsive episode following which basal sedation is maintained by parenteral phenobarbital. Morphine sulfate in doses of one quarter of one-half grain are used to supplement the basic sedation and is a useful adjunct in bringing the unstable acute hypertensive under control.

The degree of stabilization in the control of eclampsia is indicated by stabilization of the blood pressure, the level of reflex activity, and in particular by renal function. The respiratory rate must not be depressed below 14 respirations per minute but, should depression become a problem in the face of sustained hypertension, antihypertensive drugs are cautiously employed as secondary treatment. Magnesium sulfate likewise is a useful adjunct to the morphine-phenobarbital routine. Caution, however, is urged in its use, particularly by the intravenous route or in patients with oliguria where accumulation may pose problems of magnesium retention and intoxication.

The second principle of management is to effect delivery of the patient by the simplest and least traumatic mode possible after "stabilization" of her clinical condition has been attained. Only in rare instances and in the face of dramatic clinical improvement should pregnancy be maintained. Such a course is occasionally undertaken with the hope of decreasing the hazards of prematurity for fetuses of borderline viability. No general routine can be prescribed as to how delivery should best be accomplished. In the experience of this clinic, once the acute phase of the disease has been brought under control by appropriate treatment, induction of labor by intravenous oxytocin drip (5 minims Pitocin per 500 ml. 5 per cent glucose in water) is started either to induce labor or to render the cervix favorable so that amniotomy may be perfermed. Although in obstetric matters one tends to be arbitrary, the time elected for induction of labor (or, with failure of this technique, abdominal delivery) should not necessarily be elected 24, 36, or 48 hours after the last convulsion but should be undertaken only after careful evaluation of the patient's general condition, lability of the blood pressure, the cardiovascular renal status, and careful clinical appraisal of her ability to withstand the trauma involved. Fortunately, accouchement forcé or cesarean section is no longer regarded in enlightened obstetric circles as a primary solution to the problem of eclampsia, although termination of the pregnancy plays a most significant role in the patient's management.

In the total care of the eclamptic patient a number of other somewhat obvious details come to mind. The patient should be maintained in a subdued environment where there is no undue amount of light, noise, or confusion and a minimum amount of "bedeviling with needles" as Dr. Eastman has noted. Appropriate nursing care and coordinated teamwork by the attending and resident staff are essential. Although a "toxemia team" is a luxury available only to a few larger clinics, it is extremely important that, despite daily changes of the resident and/or attending staff, treatment be integrated and does not become erratic and disjointed because of necessary rotation of personnel. Finally, oxygen administration is desirable because of the hazard of anoxia to the mother as well as the fetus. In this clinic this is supplied continuously by nasal catheter. Prophylactic digitalization, a controversial subject perhaps, is routinely accomplished as a possible aid in obviating the consequences of cardiopulmonary failure which may develop abruptly. The maintenance of reasonable caloric balance in these pitients is difficult because of the almost necessary narcotization with the management as outlined. The time-honored hypertonic glucose in limited amounts of fluid appears to have merit, not only in providing calories but also in possibly protecting the liver from injury secondary to the generalized vascular manifestations of the disease from which the liver is not exempt. In view of large amounts of body water that may be sequestrated in the extravascular compartments, fluid administration should be limited even in the face of hemoconcentration. Vigorous attempts to correct hemoconcentration may result in disaster upon release of fluid from the extravascular compartment at some point in the evolution of the disease. Needless to say, cautious correction of anemia by whole blood transfusion or administration of packed cells is desirable.

It is quite apparent from the foregoing commentary that the rather sophisticated management of the patient in question is at variance with my philosophy in at least one significant detail: maintenance of pregnancy in the face of eclampsia. Admittedly, one must be cautious of criticizing clinical management which produces satisfactory results. However, individual routines may prove to be improper when analyzed statistically after application to a significant number of patients, and any bizarre approach to disease may occasionally meet with success because of an unusual resistance of the patient.

In reviewing this patient's protocol one must conclude that her response to therapy was not dramatic despite the fact that convulsions were controlled. In this regard, the record is somewhat contradictory: "rapid and sustained improvement" is not consistent with "more difficult to control . . . blood pressure . . ." as pregnancy progressed. After initial and reasonable stabilization it is felt that termination of the pregnancy should have been effected. The persistence of proteinuria of rather marked degree during the 2 weeks prior to delivery suggests on the basis of recent evidence that permanent kidney injury may have been sustained. For an unspecified period of time urinary output was maintained only by the administration of intravenous chlorothiazide, oliguria developing when this diuretic agent was discontinued. Even after the establishment of diuresis later in the patient's hospital course

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her blood pressure became increasingly difficult to regulate. These observations are consistent with the view that acute toxemia can be "controlled" but cure occurs only after delivery.

The corollary to the problem posed by the pathologic physiology of the kidney in toxemia is that of placental function. At the present state of our knowledge, assessment of placental function is not possible and the calculated fetal risk in the individual case is difficult to assess. There doubtless exists a spectrum of placental failure or decompensation in cardiovascular-renal diseases complicating pregnancy that existing techniques are incapable of detecting although the end point is definite and easily diagnosed-fetal death. Prolongation of pregnancy in the interest of fetal maturation is not therefore necessarily beneficial to the fetus in utero and may indeed impose additional hazards to fetal existence in view of the well-established occurrence of placental pathology in toxemia. Accordingly, maintenance of pregnancy must be undertaken with caution once the disease has been controlled in the mother. In my opinion the management of the case presented is seriously at variance with established obstetric practice in this regard. Moreover, remote prognosis for the mother in terms of persistent hypertension after delivery appears to be related to the duration of the acute episode, an additional indication for termination of the pregnancy.

In the management of acute toxemia clinical symptoms and signs are necessarily used as guide posts in assessing clinical response although no clinician is infallible in predicting success. The necessary empiric approach to correction of symptomatology is prescribed by our present limited understanding of the pathologic physiology of toxemia. However, one may be misled by too great absorption in isolated symptomatic phenomena when the over-all condition of the patient is not considered and when the basic underlying disease process is uncertain but persistent. It would appear that with attention directed to only certain parameters

of "control" a sense of clinical security made carrying of this patient's pregnancy permissive.

A number of minor criticisms in the maiagement of this patient may be mentioned. The dosage of magnesium sulfate was limited in this case to the point where it was of questionable value therapeutically. In our usage, 10 Gm. initially by intramuscular injection and 5 Gm. intramuscularly at 6 hour intervals would be considered adequate. However, in the face of oliguria the use of magnesium would be undertaken with extreme caution and with calcium gluconate immediately available should evidence of magnesium intoxication develop. No mention is made of oxygen administration in the initial treatment of this patient, an adjunct that may be very beneficial in the potentially convulsive patient. With techniques for rapid administration of digitalis available the matter of prophylactic use of digitalis may be questioned. However, the patient with severe pre-eclampsia or eclampsia or organic heart disease and incidental toxemia would be given digitalis prophylactically in this clinic.

In summary, it is felt that prolongation of the pregnancy in this patient was not justified, either in the interest of the fetus, in possible jeopardy because of actual or potential placental pathology, or in the interest of the mother whose clinical course during the 2 weeks' hospitalization cannot be interpreted as truly satisfactory. Continued exposure of the mother to the milieu of toxemia may in addition have altered her remote prognosis for hypertension.

Charles P. McCartney, M.D.

Chicago, Illinois

Professor, Department of Obstetrics and Gynecology,

University of Chicago School of Medicine and Chicago Lying-in Hospital

The management of this case was highly successful. A healthy infant was delivered, and this 16-year-old mother left the hospi al in good condition without a uterine scur.

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The approach to this problem was logical. The convulsions were controlled, diuresis was established, and, in the presence of what was interpreted as sustained improvement, medical therapy was continued until clinical judgment, based upon maternal and fetal considerations, indicated that the opportune time for delivery had arrived.

Parenteral chlorothiazide played an important role in the treatment of this patient. The benzothiadiazine drugs can cause a serious electrolyte imbalance when they are used intensively. Under these circumstances, it is imperative that their dosage be controlled by serial serum electrolyte determinations and that supplemental potassium be given as was done in this case.

Diuretic and antihypertensive drugs are not substitutes for anticonvulsants in the prophylaxis and management of eclamptic seizures. When 50 per cent magnesium sulfate is administered intramuscularly for this purpose, an initial amount of the order of 12 ml. is preferable to the smaller dose which was employed in this case.

In some instances, the rate of progress of pre-eclampsia-eclampsia can be modified by medical therapy and termination of the gestation can be delayed until the delivery of a viable infant is probable or until vaginal delivery can be accomplished. Nevertheless, there is no assurance that the clinical improvement achieved by medical treatment can be sustained. The maternal and fetal risks inherent in this disease persist as long as placental function is maintained and the presence of intercurrent eclampsia does not preclude intrauterine fetal death, the occurrence of abruptio placentae, a recurrence of convulsions and coma, and the ultimate death of the patient. Frequent re-evaluation of the rate of progress of the disease, utilizing all possible criteria, is, therefore, essentiel.

Many potentially critical biologic changes are present in this entity, and a single favorable prognostic sign does not necessarily denote sustained improvement. One should not be misled by a satisfactory response to antihypertensive or diuretic therapy and ig-

nore the implications of increasing proteinuria, advancing retinopathy, or other signs and symptoms indicative of a progression of the disease. The magnitude of the urinary protein excretion is a valuable criterion and one criticism of the management of this case, if this is justified in view of the satisfactory result, is that the estimate of sustained clinical improvement was not corroborated by quantitative 24 hour urinary protein determinations.

Cerebral hemorrhage is a major cause of death in eclampsia. In the Chicago Lying-in Hospital series, 50 per cent of the deaths from convulsive toxemia have been due to this complication. Previously normotensive gravidas whose systolic blood pressures rise to 180 mm. Hg or more are candidates for a cerebrovascular accident, and a rapid lowering of the blood pressure and its maintenance at moderate hypertensive levels is desirable in the prophylaxis of this complication. This can usually be accomplished by the administration of reserpine, hydralazine, and one of the veratrum derivatives. One wonders, therefore, if a more precise control of this patient's hypertension could not have been achieved.

When the cervix is not ripe or the infant is premature, the management of intercurrent eclampsia taxes the judgment of the physician. He has to evaluate the fetal and maternal risks in prolonging the gestation and weigh these against the neonatal hazard of immaturity and the desirability of vaginal delivery. The signs, symptoms, and laboratory findings upon which this evaluation is based are often subject to varied interpretation and the conclusions which are drawn from them are prejudiced by the obstetrician's experience. If the results are satisfactory, his judgment is vindicated, as it was in this case. If a viable infant succumbs in utero, if a premature infant dies in the neonatal period as a consequence of immaturity, or if a major maternal complication develops during the course of this disease, it is criticized.

In this case the lack of a favorable blood pressure response to antihypertension ther-

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apy contradicted the impression of sustained improvement and was a major factor influencing the decision to terminate the gestation on this patient's fifteenth hospital day. This was evident early in the course of the disease and indicated that the risk of intrauterine fetal death was great. Many obstetricians, among whom I have included myself, would have concluded that the fetal and maternal risks in prolonging this gestation outweighed the hazard of immaturity and the desirability of vaginal delivery. They would have terminated the pregnancy on or before the fifth hospital day, preferably by amniotomy and the induction of labor or by a low cesarean section within 18 to 20 hours after rupturing the membranes, if the attempted induction failed.

The convulsive state which is designated as eclampsia results from a progression of the biologic changes which characterized true toxemia of pregnancy and is but one manifestation of the severe form of this disorder. The imminence of this complication is usually reflected in the clinical course of the disease and eclampsia is preventable with few exceptions provided the patient seeks prepartum care and follows the advice of her physician.

The maternal mortality in eclampsia approximates 7 per cent with an institutional range of 0 to 17 per cent and the fetal hazard in this complication is equally great. The major causes of death in eclampsia are cerebral hemorrhage, cardiac failure with pulmonary edema, and complications of operative obstetrics. Hepatic necrosis and hemorrhage, adrenal hemorrhage, peripheral circulatory collapse, respiratory complications, and renal failure are infrequent causes of death.

Oliguria and anuria with moderate degrees of nitrogen retention, which are rapidly reversed following delivery, are often present in this disorder, but pronounced azotemia rarely occurs in the absence of acute tubular or renal cortical necrosis. In the Chicago Lying-in Hospital series, these complications were not initiated by the disease but resulted from transfusion of incompatible

blood and from renal ischemia caused by hemorrhagic shock.

As a consequence of the muscular activity and the abnormal pulmonary exchange which accompany the convulsive state, blood lactic acid and the total organic acid are increased and bicarbonate is decreased. Plasma pH is often reduced after a convusion but tends to return to normal when adequate respiration is established. Repeated convulsions may result in an uncompensated alkali deficit, a sustained lowering of the pH and persistent acidemia. Hypovolemia in the presence of an increased volume of extravascular fluid occurs in the severe form of this disease. This is manifested by an elevated hematocrit determination, may accompanied by potentially serious changes in serum electrolytes, and can result in medical shock. The failure of treatment to effect hemodilution constitutes an unfavorable prognostic sign. These physiochemical changes contribute to the maternal and fetal risks inherent in this disease.

The patient with eclampsia should always be regarded as being critically ill and if the physician is not experienced in the management of this disorder he should obtain consultation without delay.

In the management of eclampsia one controls the convulsions, establishes diuresis, lowers the blood pressure, and terminates the pregnancy at the time and by the method which present the least maternal and fetal risk under the specific circumstances.

The constant attention of skilled personnel plays an important role in the management of this disease. Extraneous stimuli are minimized. A mouth gag and a retention catheter are employed. Temperature, pulse rate, respiration, and urine volume are determined every 2 hours because of their prognostic value. Oxygen is used for cyanosis. Intermittent suction is employed to maintain a clear airway and infrequently a tracheotomy may be necessary to ensure adequate respiratory exchange. Nothing is given by mouth if the patient is unconscious. After the patient regains consciousness, a low-salt diet is instituted.

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For the control of the seizures, we employ a: least two, preferably the first two, of the fellowing drugs: (1) 12 ml. of 50 per cent magnesium sulfate solution intramuscularly, then 6 ml. intramuscularly after each convulsion or every 4 to 6 hours when the convulsions are controlled (an attempt is made to limit the maximum amount of this drug to 40 ml. in 24 hours); (2) 0.25 to 0.5 Gm. of amobarbital sodium subcutaneously every 4 to 8 hours; (3) 3 Gm. of chloral hydrate in 100 ml. of starch water rectally every 12 hours; (4) 30 ml. of paraldehyde diluted with oil, rectally; (5) 16 mg. of morphine sulfate intravenously, repeated until convulsions cease or respirations become 12 per minute. Morphine is the least desirable of the drugs listed. As a rule it is used only for sedation when the patient is in active labor.

Chlorothiazide and hypertonic glucose are employed to establish and maintain diuresis. If one elects to use chlorothiazide, it must be administered parenterally while the patient is unconscious, and its intensive administration by either the intravenous or oral route necessitates serial serum electrolyte determinations and the administration of supplemental potassium for the prevention of serious electrolyte disturbances.

It has been our experience that chlorothiazide and similar drugs are relatively ineffective when hemoconcentration, which characterizes the severe form of this disease, is present but become effective once hemodilution has been achieved either by the use of salt-free plasma albumin or hypertonic glucose. Because of the cost of this serum protein fraction, we prefer to use the latter.

When hypertonic glucose is employed, 1,000 ml. of a 20 per cent solution is administered two to three times daily with the object of obtaining a urinary output of at least 30 ml. per hour. The entire amount is given within 30 to 50 minutes. If the defired diuresis is not achieved with 1,000 ml. of 20 per cent glucose, 500 ml. of 30 per cent glucose is substituted. In the presence of anuria or cardiac failure, 100 or 200 ml. of 50 per cent glucose solution is used.

Solutions containing electrolytes are, in general, contraindicated.

The antihypertensive drugs afford an effective means for maintaining the blood pressure at mild hypertensive levels without resorting to large amounts of sedative and narcotic drugs which increase neonatal mortality. These agents are not substitutes for the anticonvulsion action of magnesium sulfate and are not curative.

A combination of reserpine, hydralazine hydrochloride, and cryptenamine acetate are used. It is our practice to administer 2.5 mg. to 5 mg. of reserpine intramuscularly and repeat this drug every 8 to 12 hours, if necessary. An intravenous drip containing 20 mg. of hydralazine hydrochloride, 2.5 to 5 mg. of cryptenamine acetate and 500 ml. of 20 per cent glucose are administered. The drip is started at the rate of 15 drops per minute and the rate of flow adjusted to maintain the blood pressure in the desired range. Continuous blood pressure recordings are made until the pressure is stabilized; subsequent determinations are made at intervals of 15 to 20 minutes. This drip may be maintained for 24 hours or longer. It may be discontinued when the hypertensive crisis has been resolved, and cryptenamine acetate administered intramuscularly in doses of 0.25 to 0.5 mg. to maintain the blood pressure at mild hypertensive levels.

Hydralazine alone may be administered by a continuous drip or intermittent intravenous injection. The initial dose of hydralazine by intermittent intravenous injection is 10 to 20 mg. The initial and subsequent dosage and the frequency of administration are determined by the blood pressure response and the duration of effect. Twenty milligrams of hydralazine diluted in 20 ml. of 5 per cent glucose solution is injected at the rate of 0.5 ml. per minute. After the first 20 mm. fall in systolic blood pressure, the injection is halted for 2 or 3 minutes and resumed with frequent interruptions until the desired level, which in eclampsia approximates 140/90, is achieved. Continuous blood pressure recordings are made during this period. Subsequent determina-

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tions are made at intervals of 15 to 20 minutes. The drug is not repeated until the blood pressure rises.

The patient with heart failure and pulmonary edema is given digitalis, oxygen is administered, and hexamethonium is employed to decrease central venous pressure. Fifteen milligrams of hexamethonium in 20 ml. of 5 per cent glucose is injected slowly while continuous blood pressure determinations are made to avoid overdosage. This initial dose can be increased and repeated every 30 minutes until the desired decrease in central venous pressure is obtained. The response to this ganglionic blocking agent is enhanced by a semirecumbent position. For maintenance therapy, hexamethonium is given intramuscularly every 2 to 4 hours. Subsequent dosage and frequency of administration are determined by the blood pressure response and the duration of effect.

The lowest mortality in mild eclampsia is achieved by medical treatment and induction of labor when the cervix is ripe. Nevertheless, delay in terminating the pregnancy increases the fetal risk. Because of this, we hesitate to prolong the medical treatment of intercurrent eclampsia beyond 5 days. In those instances where it is desirable to do this, we believe that re-evaluation of the case on an almost hourly basis, utilizing all possible criteria, is imperative.

The maternal mortality in severe eclampsia is still 35 per cent. In our experience, these patients have recovered only if delivery or intrauterine death occurred early in the disease. During the past two decades we have had no deaths from eclampsia. This is attributable to a precipitous decline in our incidence of the severe form of this disease. Severe eclampsia is characterized by the presence of any one of the following signs or symptoms:

- 1. More than 10 convulsions.
- 2. Coma of 6 or more hours.
- 3. Temperature of 102.5° F. or higher.
- 4. Pulse rate of 120 per minute or more.
- Respiratory rate of 40 per minute or more.

- 6. Evidence of cardiovascular impairmen:
 - a. Pulmonary edema.
 - b. Cyanosis.
 - c. Low or falling blood pressure.
 - d. Low pulse pressure.
- 7. Failure of the treatment to:
 - a. Stop the convulsions.
 - b. Produce a urinary output of at least 30 ml. per hour or 700 ml. in 24 hours.
 - c. Produce a hemodilution as evidenced by 10 per cent decrease in the hematocrit or serum protein concentration

If the patient with severe eclampsia is in labor, delivery is hastened by rupturing the membranes. If the patient is not in labor, within 8 to 12 hours after the convulsions are controlled and diuresis is established: (1) labor is induced if the state of the cervix is such that vaginal delivery can be anticipated within 18 to 24 hours; (2) cesarean section is performed, preferably under local anesthesia, if the cervix is not ripe, if induction fails, if an inertial labor results from the attempted induction, or if there is an obstetric indication for abdominal delivery.

The biologic abnormalities which accompany eclampsia are rapidly reversed following delivery and residual damage or a recurrence of this disease in subsequent pregnancies is infrequent in our experience.

In the postpartum management of eclampsia, magnesium sulfate, diuretic agents, antihypertensive drugs, sedation, and a salt-poor diet are employed as previously outlined. Diuretics are administered until the physiologic diuresis begins. This diuresis, which is a valuable prognostic sign, usually appears within 12 to 24 hours after delivery but may be delayed as long as 72 hours.

Editor's comment

The Consultants have brought out two points worthy of emphasis. The results obtained in one case cannot be construed to be indicative of the course of other patients who have eclampsia and one is best guided by the average expected or known result of management. Termination of pregnancy ol-

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t vo obd to ients i-led t of lewing correction of the acute aspects of this condition is imperative. Permitting the gestation to continue is dependent upon sustained improvement and in the case in point this did not pertain. The decision of the time to terminate the pregnancy is based upon evidence which indicates lack of sustained improvement and on occasion this may be indicated by a single finding. Prompt delivery is more advantageous to both the mother and the infant in most instances and this should be the general guide to management.

Editorials

The Pacific Coast Obstetrical and Gynecological Society

THIS number of the JOURNAL includes for the first time the papers read before the Pacific Coast Obstetrical and Gynecological Society. These were presented before the Twenty-seventh Annual Meeting of the Society held in Yosemite National Park, California, on Sept. 28 to Oct. 1, 1960.

In his Presidential Address, appearing as the opening article in this number, Dr. George Judd has referred to the beginnings of the Society, some of its accomplishments and its aspirations for the future. The Editors wish to take this occasion to give a word of heartiest welcome and to express their own satisfaction that the Pacific Coast Society has joined the sponsoring organizations for the JOURNAL.

A. B.

J. B.

H.T.

The research training grants program in developmental biology, 1961:

IN 1953 there was formed a new study section of the National Institutes of Health to review grant requests for research in the field of human embryology and development. The area as then conceived comprised the disciplines of obstetrics and gynecology, pediatrics, and certain basic science specialties dealing with reproduction. At that time there was a significant research lag in the entire field of developmental biology. This was particularly true of departments of obstetrics and gynecology, where there was a marked deficiency in research resources. The establishment of a special study section in any

field is usually accompanied by a great increase in research grant requests and productivity in its special area of interest. The results in the field of human development more than lived up to the fondest hopes of the study section. The total dollar value of grants awarded rose from \$300,000 in 1953 to \$8,330,000 in 1960. As far as departments of obstetrics and gynecology were concerned there were 26 projects in 1953 with the value of \$225,123 and 136 projects at \$2,664,115 in 1960.

Such progress can be reviewed only with satisfaction. However, the availability of such

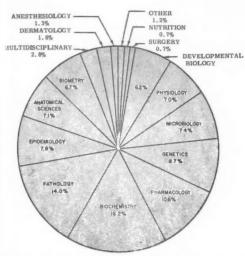


Fig. 1. Distribution of total expenditures in the general research training grants program for year 1960, by discipline.

research funds created a severe demand for the few investigators with sufficient training and background to utilize this money both well and wisely.

This lack of qualified personnel was particularly acute in departments of obstetrics and gynecology which, for a number of reasons and over a good many years, had not attracted top-notch, young, full-time research personnel. Modern research problems are not simply or easily solved. The very design of research problems and the tools necessary for their accomplishment in the field of reproduction require a good deal of sophistication and thorough knowledge of the basic disciplines often beyond the reach of the personnel of many departments of obstetrics and gynecology. As a matter of fact, there are but a handful of departments with personnel sufficiently trained to be able to carry forward modern and meaningful research. More and more one hears the statement that personnel, not money, constitute the leading obstacle for research progress in our specialty.

With considerable foresight, in 1958 Congress authorized and the National Institutes of Health embarked upon an expansion of training programs in basic sciences. Embryology and development was considered among the most needful areas and in 1959

a special ad hoc committee was constituted to review training programs in developmental biology originating in departments of obstetrics and gynecology, pediatrics, and the basic disciplines of embryology and zoology. As a primary precept these grants were not to be used for clinical training but for training in basic science disciplines. They were to be awarded to postdoctoral personnel either after or during an interruption of their residency training in order that they could obtain fundamental scientific knowledge and techniques so necessary if they were to pursue an academic career in their specialty.

Table I. Number of research training grants approved by department and year

Department	1959	1960
Obstetrics and		
Gynecology*	5	31
Pediatrics	5	8
Biology and Zoology	3	3

*Two grants awarded in 1958.

†One grant approved final 1961.

Table II. Active training grants in departments of obstetrics and gynecology

Program director	Place	No. of first year trainee stipends (fulltime)		
N. S. Assali	University of California,			
Ernest Page	Los Angeles University of California, San Francisco	2		
C. Lee Buxton	Yale University	2		
Louis M. Hellman	State University of New York	2		
Duncan Reid	Harvard Uni- versity	2		
Joseph Seitchik	Hahnemann Medical College	1		
Gordon Wat- kins Douglas	New York University	2		
Howard C. Taylor, Jr. Seymour Lieberman	Columbia University	2		
Roy G. Holly	University of Nebraska	3		
Curtis J. Lund	University of Rochester	2		

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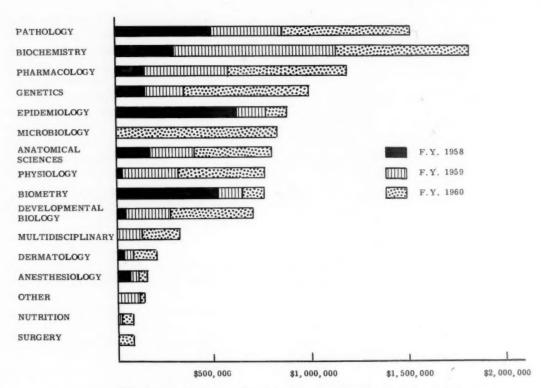


Fig. 2. Growth of general training grant program by discipline and fiscal year.

The objective of most of these programs was not to furnish a man with a single technique whereby he could make limited scientific accomplishments but to furnish him a scientific background sufficiently broad so that he would be able to take part in the rapid and complex developments of research of the future. These programs as they have developed are often removed from the particular clinical specialty and are located in basic science departments. Many are Ph.D. directed—not that this goal is always desirable or often achieved.

A beginning in research training programs has been made and while it is too early to assess the results, there are indications that these programs will have a sound effect on the academic departments of obstetrics and gynecology throughout the country. There is no question that we as a specialty have lagged behind our colleagues, particularly in departments of medicine, in modernization of our scientific development and research. Through these training programs we have

been given a chance to catch up and to forge ahead. A glance at Table I shows the progress that has already been made.

Close to a half million dollars was recommended for approval in 1960 as compared with \$360,000 in 1959—an increase of 42 per cent. The average grant is now about \$36,000 yearly and extends over a 5 year period. The relative importance of the training programs in developmental biology as they relate to the over-all training program is seen in Fig. 1. More impressive is Fig. 2, which shows the relative growth of the individual programs. The projected growth of the developmental biology program will give a total of just under one million dollars for the year 1961.

There are now available 20 beginning stipends for basic science training in our specialty (Table II). These are open to all who are qualified and care to apply. They represent exceptional opportunities for basic research training with full and adequate financial support.

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The members of the committee that initiated this program and who carry on the reviews of the various grant requests are convinced that this effort is one of the most important and worthwhile in which they have engaged. They feel that its success is vital to the growth of our specialty and basic to the health and vitality of our nation. From

the roles of the trainees in this program will come our future departmental chairmen, our research leaders, and, above all, those who can make the field of developmental biology one that will attract young men of high caliber. We are proud to present this promising embryo for your consideration.

Louis M. Hellman

Correspondence

Vulvar carcinoma

To the Editors:

In many reports concerning treatment of vulvar carcinoma, 5 year salvage rates vary from 40 to 60 per cent, but in almost every series in which nodes were removed the "cure group" and the "node-free group" are practically identical. It is only with the supraradical vulvectomy and nodectomy that salvage has improved in more recent studies. This operation is indicated only in approximately half the patients. The problem, therefore, is to properly select patients for radical operation.

Our dye studies, rechecked, have demonstrated that the nodes adjacent to and under the inguinal ligament (Cloquet's or Rosenmueller's node) are always involved first. If these nodes are not stained, there is no dye in either deep or superficial femoral or iliac nodes on either side.

With this thought in mind, I would ask all

groups performing operations for vulvar carcinoma to resect Cloquet's node first as a separate specimen before they proceed to their further definitive therapy.

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It should not be too long before my thesis is verified or disproved clinically. If proved, the first step after the diagnosis has been confirmed will be a bilateral removal of the infrainguinal nodes. If these are negative, the patient will have an excellent chance for completé cure with simple radical vulvectomy and removal of the entire local lesion. Otherwise, she will require treatment directed to all nodal areas in addition to that concerning the local lesion.

I am willing to act, temporarily at least, as a clearinghouse for reports from interested groups. Eduard Eichner, M.D.

10605 Chester Ave. Cleveland 6, Ohio March 16, 1961

Reviews | Abstracts

Edited by LOUIS M. HELLMAN, M.D.

Reviews of new books

Facts for the Childless Couples. By E. C. Hamblen. Second edition. 130 pages, 13 figures. Springfield, Illinois, 1960, Charles C Thomas, Publisher. \$3.50.

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The laity without a scientific background beyond the usual high school biology course have difficulty with many of the books on the subject of human reproduction and its complexities supposedly written just for them. However, Facts for the Childless Couples presents the pertinent information with such clarity and accuracy that the husband and wife can become oriented to the types of examinations and treatments employed by the doctor to solve their problem. The author outlines the genital and endocrine systems of the male and the female in understandable fashion.

Some popular misconceptions and practical suggestions are discussed in another section of the book. In the final portion of this monograph some new fertility facts and fads are presented in a realistic manner.

Perhaps the author could have given a little space and more attention to the causes and prevention of miscarriages. In addition an index would be of assistance to the reader who desires to refer to the book from time to time when a particular question enters his mind. Dr. Hamblen's belief that the economically strained couple should postpone investigation of their infertility until fiscal "well-being" is debatable.

Mitra Operation for Cancer of the Cervix. By Subodh Mitra. 93 pages, 38 figures, 13 tables. Springfield, Illinois, 1960, Charles C Thomas, Publisher. \$6.00.

The author, long an advocate of radical vaginal hysterectomy for the treatment of carcinoma of the cervix, has evolved an operation which he

feels combines certain advantages of the Schauta procedure with elimination of its main criticism-failure to remove the deep pelvic lymph nodes. His operation is done in two stages at one sitting. It starts with extraperitoneal pelvic lymph node dissection through bilateral suprainguinal incisions. During the first stage he performs, in addition to lymph node dissection, certain steps, namely, ligation and section of the ovarian vessels; ligation and section of the uterine arteries at their origins; partial dissection of the ureteric canals; partial blunt dissection of the paravesical and pararectal spaces -which make the second stage of the procedure simpler and more secure than when the Schauta procedure is done alone.

The author feels that this procedure accomplishes everything that the Wertheim operation does and cites that it is particularly good in Stage II cases where there is vaginal extension of the lesion. It seems to this reviewer that the author's procedure has one disadvantage over the Wertheim technique—inadequate exploration of the abdomen prior to embarking on an extended procedure which, in the case of metastasis located beyond the operative field, is doomed from the start.

After a brief introductory chapter, there are very short sections on preoperative investigation of the patient and anesthesia techniques as used at the author's clinic. The vast majority of the book is devoted to the steps of the operative procedure, including specific and worthwhile points of caution stressed in the appropriate places as the dissection proceeds. There is no section devoted to anatomy per se, so that it is imperative that the reader be familiar with the pelvis and its contained viscera. This is particularly true as many of the plates are only fair.

The last sections are devoted to the statistics of Dr. Mitra's operation. The 5 year cure rates in 20 cases of Stages I, II, and III are 70 per cent, and in 16 cases of Stages I and II are 75 per cent, these having been treated in the years 1949 to 1951.

Fluid Balance in Obstetrics. By Philip Rhodes.

169 pages, 12 tables, 4 figures. Chicago,
1960, Year Book Publishers, Inc. \$5.75.

The elements of water and electrolyte metabolism are outlined in an admirably lucid style.

The book is addressed to the practicing physician and can be commended to him. In the preface, the author writes: "The purist in physiology . . . may well be disappointed by obvious omissions . . . ," and it would not be fair to dwell on these.

On page 32 the average total weight gain in pregnancy is given as 24 pounds, with a standard deviation of 10.8 pounds. "This means that two-thirds of normal women will gain less than 13 lbs." This slip is corrected on page 34—one sixth is the proportion. It seems doubtful that the blood volume is greater in midpregnancy than at term (page 39). In the discussion of water and sodium retention in normal pregnancy, no mention is made of the serial studies made by Plentl's group or by Haley and Woodbury. On page 52: "The serum protein-bound iodine, too, is increased, and this is a direct measure of thyroid activity." However, the increased bound iodine probably does not reflect increased thyroid activity, for the binding is so tight as to preclude much utilization of the extra hormone. On page 85, the concept of glomerular intermittence rears its hoary but defunct head. On page 92, the protein content of edema fluid is said to be 0.24 Gm. per milliliter (about four times the plasma level) and a miscalculation of the total amount of extravascular protein issues from this. In the discussion of fluid requirements after cesarean section, especially in toxemic patients, allowance is properly made for the abnormal amounts of fluid that had been retained in pregnancy, but in the discussion of the management of acute renal failure, where this is of far greater importance, no such allowance is made. Also, it is probably a mistake to "correct" low serum sodium levels during oliguria.

The author, after making the case for expressing electrolyte concentrations in terms of milliequivalents rather than milligrams, alternates between the two, even in the same paragraph. Fluid volumes are variously expressed in milliliters, ounces, and pints. He also follows the unfortunate convention of calling 0.9 per centualine "normal," despite his clear definition of what a normal solution is.

Enzymologie der Geburtshilfe. By Erwin Rimbach. 116 pages, 24 figures, 21 tables. 1 diagram. Jena, 1960, Veb Gustav Fischer Verlag. 17. DM.

The author briefly reviews the literature concerning certain enzymes and their variation in serum, ovaries, and the fertilized ovum. On the basis of this survey and his own work he has classified the serum enzymes as follows:

1. Specific pregnancy enzyme oxytocinase.

2. Nonspecific enzymes influenced by pregnancy: histaminase, p-polyphenol oxidase, alkaline phosphatase, acid phosphatase, betaglucuronidase, cholinesterase, lactic acid dehydrogenase, and leucine aminopeptidase.

3. Nonspecific enzymes not influenced by pregnancy: lipase, amylase, transaminase, catalase, carbonic anhydrase, and aldolase.

There is an extensive bibliography and a good index.

The greater portion of the book is a report of the author's own results obtained from analyses of serum glutamic oxalacetic acid transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum lactic acid dehydrogenase, and serum aldolase in normal and pathologic pregnancies. SGOT in the cord bloods was also compared with maternal SGOT in a number of cases. The maternal serum transaminase level was always higher than the fetal level. The failure to find any parallelism in the corresponding values was interpreted as evidence that the enzyme did not cross the placenta. Particular emphasis was placed on the association between changes in transaminase activity and icterus. Determinations of transaminase were of particular value in diagnosing disturbances of liver parenchyma associated with the various disorders of pregnancy.

Cardiac Disease in Pregnancy. By C. L. Mendelson. 385 pages, 141 illustrations, 68 tables. Philadelphia, 1960, F. A. Davis Company. \$13.50.

Why not be odious? This book suffers by comparison to Heart Disease and Pregnancy: Physiology and Management, by Burwell and Met-

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calfe, which was published in 1958. Essentially, the experience of the New York Lying-In Hospital is presented against the background of selected publications from other centers. Incidentally, the publisher's fly-leaf statement that "Dr. Mendelson has been responsible for the care of almost four thousand pregnant women afflicted with heart disease" could be true only if he had been in charge of the cardiac clinic since two years before entering medical school. This large number of patients with heart disease brings up the question of diagnosis, for the 3.7 per cent incidence is about three times that reported in other clinics in the same area. Part of the answer to this question is that the Pediatric Cardiac Clinic of the New York Hospital labels as having heart disease every child who has had rheumatic fever and, on very tenuous evidence of rheumatic fever, so labels siblings. Many of the girls in this group eventually come to the Obstetric Cardiac Clinic with the ready-made diagnosis of heart disease and this is reflected in Mendelson's remark, in a recent paper, that "nearly 75 per cent" of his pregnant women with rheumatic heart disease have mitral stenosis. What are the lesions in the other 25 plus per cent?

Bland and Jones, in a 20 to 30 year follow-up study of children with rheumatic fever at the Good Samaritan Hospital in Boston, found that only half ever developed signs of valvular lesions. Yet Mendelson, on page 82, writes that "Rheumatic fever . . . almost invariably affects the heart."

The differentiation of acute pulmonary edema from "congestive cardiac failure" is more than a matter of semantics. Both Bland and Jones and White have pointed out that in the presence of a tight mitral stenosis an increased output of the right heart will flood the pulmonary bed with more blood than can be drained through the stenotic mitral valve. The result of good myocardial function is, then, a build-up of intravascular pressure in the lungs, with transudation of fluid and pulmonary edema. Excitement or anxiety may cause tachycardia and precipitate such a crisis. Although Mendelson writes that "acute pulmonary edema poses a constant antepartum threat in tight mitral stenosis," he never comes to grip with the problem, but charges it off to "the predictable hemodynamic burden" of pregnancy and even recommends measures to increase the myocardial efficiency (page 92).

The monotonously recurring phrase "pre-

dictable hemodynamic burden of pregnancy" appears in the correlation of time of cardiac failure in pregnancy to the peak of plasma volume or peak of cardiac output. However, Gordon, in reviewing all maternal cardiac deaths in Brooklyn, found no such thing; the times of failure were distributed throughout pregnancy, with the highest incidences in the fourth month. Also ignored is the fact that the increase in blood volume is largely a "dilutional" effect in that plasma volume increases more than red cell mass. The effect of this is to decrease the apparent viscosity of the blood by 15 to 20 per cent and thus offset, partially, the burden upon the heart.

In discussing the medical supportive management of pregnant women with heart disease, Mendelson either ignores or distorts, denigrates and dismisses papers with conclusions that he finds uncongenial.

Some startling remarks are made about toxemia of pregnancy. To mention some: it is caused by placental thrombosis and infarction; it is accompanied by hypervolemia; fluid intake should be restricted; the vast majority of eclamptic fatalities associated with cerebral hemorrhage have ruptured aneurysms.

Medical and Biological Research in Israel. By Moshe Prywes. 562 pages. New York, 1960, Grune & Stratton, Inc. \$8.

In the foreword to this remarkable book concerning the accomplishments of medical and biological research in Israel, there is a statement that "Our achievements, all told, have been modest." No one reading this book could possibly agree, especially when it is found to contain 2,000 references selected from more than 5,000, most of which have been published since the foundation of the State of Israel in 1948.

The book shows how well-organized research programs encompassing a whole country can be developed within a decade. The territory of ancient Israel has always attracted the attention of European scholars, mainly because of "its theological and historical associations, so that the prerequisites were there. Saul Adler, F.R.S., has written a section entitled "Background" and has placed the development of research into three phases, (1) from the beginning of the present century to World War I; (2) the mandatory period; (3) the period from the foundation of the State of Israel to the present time. The mandatory period was important to the

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future development of research which matured after the foundation of the state. During this second phase such institutions as the Weizmann Institute of Science at Rehovot, the Technion at Haifa, and the Hebrew University of Jerusalem were founded, and their places in the world of learning and research are now well established. How the Hebrew University maintained its teaching and research activities after the enforced evacuation from Mt. Scopus is a source of continual admiration to the whole civilized world. Medical and biological education in Israel generally follow the patterns of Western methods and the Israel Medical Association is largely responsible for postgraduate medical education and the organization of symposia and medical conferences.

The bulk of the book, however, is divided into the second and third parts, one dealing with regional and applied research and the other with research of general nature. Each part is subdivided into sections which contain short descriptions of the most significant research carried out by individual departments. At the end of each section references are fully and meticulously given.

In the regional and applied research part of the book, there are chapters on public health and social medicine, plant sciences as applied to agriculture, animal husbandry, and industrial aspects of biological research.

Under the heading of "Research of a General Nature," the first section deals with experimental biology and includes references to such important subjects as genetics, radiology, and cancer research. Botany and zoology also have sections of their own. Interesting and practical information concerning the development of fishing and plant ecology has resulted from research carried out in these departments.

The section devoted to experimental and clinical research and medical disciplines covers all the major specialties and obstetrics and gynecology are included. The researches developing from the original Aschheim-Zondek pregnancy test have continued, and indigenous amphibia have been utilized for pregnancy testing. Zondek and his colleagues have made valuable contributions concerning estriol determinations in intrauterine fetal death, cervical mucous arborization, and vaginal smears for the determination of endocrine functions.

The high incidence of genital tuberculosis causing female sterility in Israel has led to ex-

tensive research by Halbrecht and his colleagues. Much work has also been done on male sterility, in particular Joel's contributions on aspermadue to obstruction, a staining method of determining the viability of human spermatozoa, and the various aspects of antibiotics on sperm motility.

Many important contributions to the American and British literature have been made by Getzowa, Sadowsky, and Laufer concerning the structure of the placenta in particular to the anuclear spaces of placental syncitium. Likewise, the work of Serr, Sadowsky, and Kohn on "nuclear sexing" and their demonstration that the placental septa are of maternal composition have received wide recognition.

A new fetal hemoglobin has been described by Halbrecht and Klibansky, and Bromberg's studies on fetal hemoglobin have been published.

The rarity of cervical carcinoma in Israel is probably responsible for the paucity of investigation into benign and malignant growths. As is well known, the incidence of cervical cancer in Israel is identical with that of Jewish women in New York, but the reasons remain obscure.

Nutritional anemia has been a great problem and is largely accounted for by the mass exodus of poorly nourished people to Israel. Some important surveys in pregnant women have been carried out, notably by Sadowsky, Izak, and Rachmilewitz, and it was concluded that anemia of pregnancy in Israel probably develops as a consequence of poor nutrition and repeated pregnancies.

This work was an enormous undertaking involving the participation of over sixty contributors under the direction of the editor, Moshe Prywes, and was sponsored and financed by the Hebrew University of Jerusalem and Hadassah, the Women's Zionist Organization of America.

Some excellent photographs of the more important research institutions add considerable interest to the book.

It is the opinion of the reviewer that all those who made this vast undertaking possible are to be congratulated.

Shaw's Textbook of Operative Gynaecology. Edited by John Howkins. Second edition. 484 pages, 428 figures. Baltimore, 1960, Williams & Wilkins Company. \$20.

The second edition of Shaw's Textbook of Operative Gynaecology having been rewritten by

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his pupil, Dr. John Howkins, successfully fulfills its stated purpose of making available standard and orthodox British practice to the apprentice surgeon.

The book has 484 pages and 428 illustrations with a format that outlines the material well, making it easy to read and follow. The photographs and illustrations are generous, descriptive, and excellent. The author has carefully and thoroughly included all phases of gynecologic practice in the text, with attention given to preoperative care, choice and technique of anesthesia, anatomy, and special medical investigations indicated prior to operation.

Separate chapters are devoted to such gynecologic disciplines as opening and closing the abdomen, postoperative treatment and complications, abdominal hysterectomy, myomectomy, carcinoma in situ of the cervix, carcinoma of the cervix, and carcinoma of the endometrium. The subjects of genital tuberculosis, endometriosis, ectopic pregnancy, tubal occlusion, and sterilization operations are also considered and discussed.

The entire section on vaginal operations, to which 9 chapters are devoted, deserves special comment because of its scope, clarity, and pertinent detailed attention to applied anatomy. Of particular descriptive uniqueness are the operations for vaginal hysterectomy, vaginal plastic procedures, rectovaginal and vesicovaginal fistulas, and stress incontinence.

Interesting and helpful chapters on surgical accidents are discussed under wounds of the bladder, ureter, intestine, and nongynecological conditions found at operation.

There are isolated instances in the textbook where the author's experiences and therapeutic approaches differ from those of others—namely, in the surgical treatment of incapacitating thronic pelvic inflammatory disease before the menopause, the author recommends conserving some ovarian tissue. However, experience has shown that this leads to a second operation in many instances in a relatively short period of time, thus seeming to indicate that a complete hysterectomy with bilateral salpingo-oophorectomy is preferable initially.

The advisability of removing cervical polyps by diathermy is open to question. Although carinomatous change in cervical polyps is rare, when these changes do occur, they usually start at the base of the polyp. Diathermy distorts the cellular pattern and makes tissue diagnosis more difficult. It would seem as though cold knife removal of cervical polyps is preferable.

The technique of packing the uterus following postabortal curettage for persistent bleeding has largely been abandoned in the United States because of sepsis, concealed hemorrhage, and its frequent failure to stop the bleeding.

The author has taken great care to include several operative procedures when therapeutic controversy exists, pointing out his preferences and his reasons. Most of the obsolete operative procedures have been omitted.

In general, Dr. Howkins has done an excellent job of revising Shaw's Textbook of Operative Gynaecology. Although no revolutionary approaches to gynecologic surgery are advanced, the book represents an honorable addition to our gynecologic armamentarium.

Ciba Foundation Symposium on Congenital Malformations. Edited by G. E. W. Wolstenholme and C. M. O'Connor. 308 pages, 91 illustrations. Boston, 1960, Little, Brown & Company. \$9.

Congenital Malformations is a 308 page volume which deals comprehensively with the factors involved in the disorganization of embryonic and neonatal development. Twelve formal presentations are offered, and these contributions are enriched and enlivened by the discussions of 29 participants who are recognized authorities in their fields. The topics covered include, among others, population studies, genetics, environmental factors, viral infections, metabolic disturbances and deficiencies, drug and chemical effects, radiation, experimental techniques, and methods for establishing the chronology of morphological and biochemical somal abnormalities.

The presentation devoted to chromosomal abnormalities is a particularly informative summary of available knowledge in this new and exciting area of human genetics. This section as well as the 24 pages of general discussion at the end, including the brief summation, are highlight features of the volume. For the interested reader, moreover, each contributor offers a valuable bibliography which includes the classic publications in the areas under discussion.

Almost all contributors referred (1) to the multiplicity of agents that can produce abnormalities; (2) to the importance of the time factor when the particular agent is administered experimentally; and (3) to the susceptibility of

early embryonic tissue to a particular noxious agent. The roles of maternal age, of the placenta, and of the "whole" environment of the mother, her nutrition and metabolism, not merely the changes in the uterus during pregnancy, were discussed as possible factors in the etiology of congenital anomalies.

The only slightly disappointing feature of this excellent volume is the paucity of material dealing with the effects of radiation on embryonal development; but it may be true, as pointed out by Hamilton in the summation, that this subject is far too big to be covered adequately in a symposium of this type.

Books received for review

- Atlas of Obstetric Technic. By J. Robert Willson. First edition. 304 pages, 55 plates. St. Louis, Mo., 1961, The C. V. Mosby Company. \$14.50.
- The Choice of a Medical Career (Essays on the Fields of Medicine). By Joseph Garland and Joseph Stokes. First edition. 231 pages. Philadelphia, 1961, J. B. Lippincott Company. \$5.
- The Conduct of Sex. By Lawrence K. Frank. First edition. 192 pages. New York, 1961, William Morrow & Co. \$4.
- Current Therapy—1961. Edited by Howard F. Conn. 806 pages. Philadelphia, 1961, W. B. Saunders Company, \$12.50.
- Die Kortikosteroid-Behandlung hamatologischer. By J. A. Horster. First edition, 108 pages, 6 tables. New York, 1961, Intercontinental Medical Book Corp. \$3.50.
- Endocrine Dysfunction and Infertility. Edited by S. J. Fomon. 86 pages, 19 figures, 10 tables. Columbus, Ohio, 1961, Ross Laboratories (Ross Conference on Pediatric Research—Report of the 35th).
- Fetal Electrocardiography. By S. D. Larks. 109

- pages, 70 figures. Springfield, Ill., 1961, Charles C Thomas, Publisher. \$6.50.
- Haimopoiesis. By G. E. W. Wolstenholme and M. O'Connor. 490 pages, Boston, 1961, Little, Brown and Company. \$11.
- Hospital Infection. By R. E. O. Williams, R. Blowers, L. P. Garrod, and R. A. Shooter.307 pages, 12 figures. Chicago, 1960, Year Book Publishers, Inc.
- Multiple-Choice Examinations in Medicine. By J. P. Hubbard and W. V. Clemans. 186 pages. Philadelphia, 1961, Lea & Febiger. \$3.75.
- Practique Obstetricale. By B. Jamain. Third edition. 277 pages. Paris, 1960, L'Expansion.
- A Student's Guide to Obstetrics and Gynaecology. By C. J. Dewhurst. 229 pages, 19 figures. Philadelphia, 1961, J. B. Lippincott Company. \$4.
- Systemic Lupus Erythematosus. By D. L. Larson. 212 pages, 2 illustrations, 15 tables. Boston, 1961, Little, Brown & Company. \$7.50.
- You'll Live Through It. By Miriam Lincoln. 221 pages. New York, 1961, Harper & Brothers. \$3.50.

Selected abstracts

The Lancet

Nov. 12, 1960.

*Bloise, W., deAssis, L. M., Bottura, C., and Ferrari, I.: Gonadal Dysgenesis (Turner's Syndrome) With Male Phenotype and XO Chromosomal Constitution, p. 1059. Bloise et al.: Gonodal Dysgenesis (Turner's Syndrome) With Male Phenotype and XO Chromosomal Constitution, p. 1059.

A boy of 8 years had a bifid "scrotum" and 2 small urethral meatuses. At operation a rudimentary uterus and an undeveloped testis, but no ovarian tissue were found. The nuclear

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ex (blood and oral smears and material from skin biopsy) was male. Chromosomal counts culture of bone marrow cells) showed that here were only 45 chromosomes present. Pairing of the chromosomes led to the belief that either the other X chromosome or the Y chromosome was necessary. The conclusion was reached that XO chromosomal constitution is not incompatible with a male phenotype and the presence of an embryonic testis.

David M. Kydd

Obstetrics and Gynecology of the USSRt

No. 1, January-February, 1960.

*Lapin, L. N., Ioffe-Golubchik, G. I., and Priev, I. G.: The Use of Microelements in Functional Uterine Hemorrhages, p. 91.

Lapin, Ioffe-Golubchik, and Priev: The Use of Microelements in Functional Uterine Hemorrhages, p. 91.

Eighty-nine patients with menopausal hemorrhages and 20 patients with juvenile hemorrhages were treated with solutions of sulfate salts of copper, cobalt, and manganese in a dosage of 5 to 6 mg. of each of these elements daily. In 77 patients of the first group the results were very satisfactory, in 6 the results were doubtful, and in 6 no effect was obtained. In the second group (the juvenile group) very good results were obtained in 17. In 2 patients the hemorrhage recommenced; however, repeated administration of the elements was effective. Research data published by the Department of Chemistry of the Medical School in Samarkand indicate that severe forms of anemia are connected with changes in the metabolism of copper, and the intake of small amounts of copper or copper together with cobalt and manganese given to animals produced very satisfactory

Because of the satisfactory results with the animal experimentations, the above elements were administered to a group of patients as indicated above and results were good.

Jacob Solome

†The Book Review and Abstract Editor is pleased to announce an exchange between the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY and Obstetrics and Gynecology of the USSR, Dr. Mihaeloff, Chief Editor. 1961 is the thirty-seventh year of bimonthly publication of this journal. Currently the articles each have a concise English summary. We will publish a table of contents and an abstract of one or two important articles.

No. 2, March-April, 1960.

*Shimanovsky, R. N., and Wermel, E. M.: On the Treatment of Ovarian Cancer with NN'N"-Triethylene Thiophosphoramide (thio-TEPA), p. 108.

Shimanovsky and Wermel: Treatment of Ovarian Cancer With NN'N"-Triethylene Thiophosphoramide, p. 108.

Thirty patients with ovarian carcinoma of the III and IV stages were treated with thio-TEPA. In Stage III remission of up to one year is achieved. In some cases the tumor and infiltrates diminish in size and become operable. Dosages of 200 to 300 mg. per course are recommended to attain a long-term remission. The best results were obtained by giving two consecutive courses of thio-TEPA with a 1½ to 2½ month interval, especially in instances where after the first course operation can be resorted to.

In the treatment of the Grade IV cancer and Krukenberg's tumor, the results were unsatisfactory, evidently because of insufficient doses of thio-TEPA.

Thio-TEPA was also found effective in cases of relapse following operation.

The authors also suggest that thio-TEPA for Stage I and II ovarian cancer, instituted immediately after a radical operation, would increase the rate of recovery.

Jacob Solome

No. 3, May-June, 1960.

*Vanina, L. V.: Pregnancy and Labor in Women Following Commissurotomy, p. 99.

Vanina: Pregnancy and Labor in Women Following Commissurotomy, p. 99.

Twenty gravidas were kept under observation following heart operations (1958-1959). Eighteen of them underwent mitral commissurotomy (in one recommissurotomy was performed), in 2 mitroaortal commissurotomy was performed. Sixteen patients were operated on prior to pregnancy and 4 during gestation. The pregnancy was terminated with delivery in 14 women, in one with spontaneous late abortion, in another with induced abortion; 4 women were still pregnant at the time of the report. One patient died of cardiac insufficiency on the twelfth day after cesarean section.

In final evaluation, where the commissurotomy results are considered excellent or good, the outcome of pregnancy and labor is favorable. In patients where the results are questionable, pregnancy and labor are contraindicated.

Jacob Solome

Items



American Board of Obstetrics and Gynecology

Applications for certification in the American Board of Obstetrics and Gynecology, new and reopened, Part I, and requests for re-examination in Part II are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Aug. 1, 1961. No applications can be accepted after that date.

Candidates are requested to write to the office of the Secretary for a current Bulletin if they have not done so in order that they might be well informed as to the present requirements. Application fee (\$35.00), photographs, and lists of hospital admissions must accompany all applications.

After July 1, 1962, this Board will require a minimum of 3 years of approved progressive residency training to fulfill the requirements for admission to examination. After the above date, training by preceptorship will no longer be acceptable.

Diplomates of this Board are urged to notify the office of the Secretary as soon as possible of changes in address.

> Robert L. Faulkner, M.D. 2105 Adelbert Road Cleveland 6, Ohio

Inter-Society Cytology Council

The annual scientific meeting of the Inter-Society Cytology Council will be held at the Hotel Peabody, Memphis, Tennessee, Nov. 2-4, 1961. Dr. Paul A. Younge, 1101 Beacon Street, Brookline 46, Massachusetts, is secretary-treasurer. Everyone interested in cytology is welcome to attend.

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HOWARD C. TAYLOR, JR., Editor in Chief

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American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover,

the Journal is the official publication

of the following societies:

NEW YORK OBSTETRICAL SOCIETY
OBSTETRICAL SOCIETY OF PHILADELPHIA
BROOKLYN GYNECOLOGICAL SOCIETY
ST. LOUIS GYNECOLOGICAL SOCIETY

NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY
THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND
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Index to Volume 81

Author index

A

- AARON, JULES B., SILVERMAN, SIDNEY H., AND HALPERIN, JACOB, Fetal survival in twin delivery, 331
- ABRAMSON, MILTON, AND TORGHELE, JOHN R., Weight, temperature changes, and psychosomatic symptomatology in relation to the menstrual cycle, 223
- Acosta-Sison, H., Indications for immediate hysterectomy without curettage in cases of hydatidiform mole, 715
- Adler, Nathan H. (see Pedowitz, Pozner, and Adler), 350 Afonzo, Jose F., and de Alvarez, Russell R., Maternal isosensitization to the red cell antigen U, 45
- ALDRIDGE, CHARLES W., JR., NANZIG, REINARD P., AND BEATON, JAMES H., Uterosacral block and the obstetrical anesthesia problem, 941
- ALPERT, SEYMOUR (see BARTER, ALPERT, KIRBY, AND TYN-DAL), 493
- ALTCHEK, ALBERT (see Mendlowitz, Altchek, Naftchi, and Spark), 643
- Amorosi, Leo (see Tricomi, Amorosi, and Gottschalk), 681
- Applegate, John W. (see Moore, Morton, Applegate, and Hindle), 1175
- AREY, LESLIE B., The origin and form of the Brenner tumor, 743
- Arneson, Axel N., Continuing evaluation, 1106 (Symposium on endometrial cancer)
- AZNAR, RAMON, AND BENNETT, ALWYN E., Pregnancy in the adolescent girl, 934

T

- Bacile, Victor A., and Nagler, Willi, Unruptured primary ovarian pregnancy, 320
- BAKER, WILLIAM S., Jr., Further experience with parametrial radiogold as an adjunct to radium therapy in treatment of pelvic lymph nodes in cancer of the cervix. 797
- -, (see WALKER AND BAKER), 16
- BALDWIN, RICHARD M., WHALLEY, P. J., AND PRITCHARD, JACK A., Measurements of menstrual blood loss, 739
- Barnes, Allan C., The Australian and New Zealand Journal of Obstetrics and Gynaecology, 1071 (Editorial)
- Observer bias, 821
 The Pacific Coast Obstetrical and Gynecological Society, 1276 (Editorial)
- AND KUMAR, D., Studies in human myometrium during pregnancy. I. Electrolyte levels—preliminary report, 594
- ARON, CHARLES, Melanoma and pregnancy, 1042
- ARNS, DOUGLAS H., Suppression of postpartum lactation and prevention of breast engorgement in nonnursing mothers, 339
- ARTER, ROBERT H., ALPERT, SEYMOUR, KIRBY, TAYLOR H.,
 AND TYNDAL, CHARLES H., Cesarean section anesthesia, 493
- SEATON, JAMES H. (see Aldridge, Nanzig, and Beaton),

- Behrman, S. J., Premenstrual tension, 606 (Clinical problems)
- (see Duboff, Behrman, and Hawver), 630
- BENIRSCHKE, KURT (see RICHART AND BENIRSCHKE), 1024 BENNETT, ALWYN E. (see AZNAR AND BENNETT), 934
- BENNETT, RIDGELY C. (see CLARK AND BENNETT), 298
- Bernstine, Richard L. (see Garcia, Nelson, Bernstine, Huston, and Gartenlaub), 706
- Betson, Johnnie R., Jr., and Golden, Max L., Cancer and pregnancy, 718
- Bickers, William, Pregnancy complicated by pyocolpos, 623 (Correspondence)
- Birch, Herbert W., and Collins, Conrad G., Atypical changes of genital epithelium associated with ectopic pregnancy, 1198
- Bobrow, M. Leo, and Schreiber, Irving, Unilateral twin tubal pregnancy, 1230
- Bogen, Ben (see Hreshchyshyn, Bogen, and Loughran), 302
- Bonney, Walter A., Jr. (see Munnell and Bonney), 521 Borglin, Nils Erik, and Rappe, Adolf, Effect of estriol on breast engorgement and lactation in nonnursing mothers, 335
- BOWMAN, HERBERT S. (see SAMET AND BOWMAN), 49
- BOWMAN, JAMES (see CAMPBELL AND BOWMAN), 256
- BOYCE, C. R. (see Lebherz, Boyce, and Huston), 658 Brandy, Joseph R., and Peterson, John H., Review of
- 36 Shirodkar operations, 1191
 Brantley, William M., Del Valle, Rapael A., and
- Schoenbucher, Albert K., Pneumothorax, bilateral, spontaneous, complicating pregnancy, 42
 Bratvold, Gloria E. (see de Alvarez and Bratvold), 1140
- Bratvold, Gloria E. (see de Alvarez and Bratvold), 1140 Breese, Melvin W., Spontaneous premature rupture of the membranes, 1086
- Brewer, John I., The Australian and New Zealand Journal of Obstetrics and Gynaecology, 1071 (Editorial)
- The Pacific Coast Obstetrical and Gynecological Society, 1276 (Editorial)
- —, RINEHART, JAMES J., AND DUNBAR, RONALD W., Choriocarcinoma, 574
- Bruns, Paul (see Prystowsky, Hellegers, and Bruns), 372
- -, (see Taylor, Bruns, Dungan, and Drose), 625
- BRYANT, RICHARD D., Cesarean section in Cincinnati, Ohio. 1950-1959, 480
- Burch, John C., Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse, 281
- Burt, Richard L., and McCartney, Charles P., Management of eclampsia, 1266 (Clinical problems)
- BUXTON, C. LEE, Premenstrual tension, 608 (Clinical problems)
- —, AND HERRMAN, WALTER, Induction of ovulation in the human with human gonadotropins, 584
- Byron, Ralph L., Jr., Shipp, James F., Yonemoto, Robert H., and Chapman, Ralph, Ureterostomy in situ for temporary control of ureteral obstruction, 814

Gir

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HA

H

H

H

H

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H

H

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H

- CAHILL, JOHN J., AND ZEIT, PAUL R., Intra-arterial infusions of pelvic tumors with amethopterin, 970
- Caligara, Franco (see Rooth, Sjöstedt, and Caligara), 4 (see Sjöstedt, Rooth, and Caligara), 1
- CAMPBELL, C. GORDON, AND BOWMAN, JAMES, Enterobius vermicularis granuloma of pelvis, 256
- CAMPBELL, COLIN (see RADMAN, CAMPBELL, AND COPLAN), 344
- CARTER, JAMES E. (see HUBER, CARTER, AND VELLIOS), 560
 CHANG, NORMAN (see MORTON, MOORE, AND CHANG), 1115
 CHAPMAN, RALPH (see BYRON, SHIPP, YONEMOTO, AND
 CHAPMAN), 814
- Chappell, Clipford C. (see Page, Kamm, and Chappell), 1094
- CLARK, JOHN F. J., AND BENNETT, RIDGELY C., Uteroabdominal pregnancy, 298
- CLARK, W. H. (see Krupp, Sternberg, Clark, St. Romain, and Smith), 959
- COLLINS, CONRAD G. (see BIRCH AND COLLINS), 1198
- COOPERMAN, NORMAN R., RUBOVITS, FRANK E., AND HESSER, FRANK, Oxygen saturation in the newborn infant, 385
- COPLAN, ROBERT S. (see RADMAN, CAMPBELL, AND COPLAN),
- CRAWFORD, EDWARD J., JR., ROBINSON, LEWIS S., HORN-BUCKLE, LLOYD A., AND GODFREY, WM. E., Combined radiologic-surgical therapy of Stage I or II carcinoma of the uterine cervix, 148
- CRUMP, E. PERRY (see PAYTON, CRUMP, AND HORTON), 1009 CUSHNER, IRVIN M., Prolapse of the umbilical cord including a late follow-up of fetal survivors, 666

D

- Dandrow, Robert V. (see Tenney and Dandrow), 8
 Davis, George H. (see Frazier, Davis, Goldstein, and
 Goldberg), 988
- DE ALVAREZ, RUSSELL R., AND BRATVOLD, GLORIA E., Serum lipids in pre-eclampsia-eclampsia, 1140
- (see Afonso and de Alvarez), 45
- DEAN, ROBERT E., AND TAYLOR, E. STEWART, Postoperative morbidity from cesarean section, 877
- DEL VALLE, RAFAEL A. (see BRANTLEY, DEL VALLE, AND SCHOENBUCHER), 42
- Demetriou, James (see Langmade, Notrica, Demetriou, and Ware), 1149
- DIAMOND, BERNARD (see LEVINE AND DIAMOND), 1046
- Diddle, A. W., and Kinlaw, Stacy, Cervical carcinoma: radical hysterectomy and pelvic lymphadenectomy, 792
- —, O'CONNOR, K. A., AND JENKINS, H. H., Cervical carcinoma: growth and spread and some adjunctive therapeutic measures, 166
- DOCKERTY, MALCOLM B. (see WILSON, HUNTER, AND DOCKERTY), 546
- DOUGHERTY, CARY M., The epithelium-stroma junction in the uterine cervix, 911
- DROSE, VERA E. (see TAYLOR, BRUNS, DUNCAN, AND DROSE), 625
- Duboff, G. S., Behrman, S. J., and Hawver, D., Halochromogens in human urine associated with pregnancy and ovulation. I. Application of absorption to the iodine-color complex with particular reference to catecholamines, 630
- Dunbar, Ronald W. (see Brewer, Rinehart, and Dunbar), 574
- Dungan, Irma W. (see Taylor, Bruns, Dungan, and Drose), 625
- Dyer, Isadore, Recipe. President's address, 833
- (see ERVALL, WIXTED, AND DYER), 848

E

- EICHNER, EDUARD, Vulvar carcinoma, 1280 (Correspondence (see Root, Eichner, and Sunshine), 948
- EKVALL, LESLIE DAVID, WIXTED, WILLIAM GLEASON, AND DYER, ISADORE, Spontaneous premature rupture of the fetal membranes, 848
- Endres, Richard J., Hydatidiform mole, 711
- ESKIN, BERNARD A., LAUFER, ELIZABETH U., AND PETTIT MARY DEWITT, Hemolytic disease of the newbordue to the Good factor, 997

F .

- FAHEY, M. F. (see MARGULIS, LADD, FAHEY, AND WALSER) 840
- Faison, Jere B., Report of the maternity center association clinic, 1952-1958, 395 (Re-evaluation)
- FARRAR, H. K. JR., AND NEDOSS, B. R., Benign tumors of the uterine cervix, 124
- FAULKNER, ROBERT L., American Board of Obstetrics and Gynecology, 524 (Item)
- FISHER, JOHN J., Surgical unification of a double uterus.
- FLEMING, ARTHUR R., Abdominal exploration, 957
- FORENCE ALVAN G. A multiple biopsy technique for
- Foraker, Alvan G., A multiple biopsy technique for the demonstration of uterine serosal endometriosis, 810
- FRACHTMAN, KURT G., Granulosa-theca-cell tumor associated with endometrial carcinoma, 779
- FRAZIER, TODD M., DAVIS, GEORGE H., GOLDSTEIN, HYMAN, AND GOLDBERG, IRVING D., Cigarette smoking and prematurity: a prospective study, 988
- FRICK, HENRY CLAY (see Neumann and FRICK), 803
- FRIEDMAN, EMANUEL A., AND LITTLE, WILLIAM A., The conflict in nomenclature for descensus uteri, 817

G

- Galligan, Sylvia Jean (see Holm, Parker, and Galligan), 1000
- GAMBLE, CLARENCE J. (see TIETZE, PAI, TAYLOR, AND GAMBLE), 174
- GARCIA, NICHOLAS A., III, NELSON, JAMES H., JR., BERNSTINE, RICHARD L., HUSTON, J. WILSON, AND GARTENLAUB, CHARLES, Findings on retrograde femoral arteriography in carcinoma, 706
- GARTENLAUB, CHARLES (see GARCIA, NELSON, BERNSTINE. HUSTON, AND GARTENLAUB), 706
- GATLING, H. BEE (see Lock, GATLING, MAUZY, AND WELLS).
 451
- GLENDENING, MARY BETH, MARGOLIS, ALAN J., AND PAGE.

 ERNEST W., Amino acid concentrations in fetal and
 maternal plasma, 591
- (see GOERKE, McKean, Margolis, Glendening, and Page), 1132
- GODFREY, WM. E. (see CRAWFORD, ROBINSON, HORNBUCKLI AND GODFREY), 148
- GOERKE, R. JONATHAN, McKean, CHARLES M., MARGOLIS, ALAN J., GLENDENING, MARY BETH, AND PAGE, ERNEST W., Studies of the isolated perfused human placenta. I. Methods and organ responses, 1132
- GOLDBERG, IRVING D. (see Frazier, Davis, Goldstein, AND GOLDBERG), 988
- GOLDBERG, MARSHALL, Diagnosis of euthyroid hypometablism, 1053
- GOLDEN, MAX L. (see BETSON AND GOLDEN), 718
- GOLDFIEN, ALAN (see WOOLEVER, GOLDFIEN, AND PAGE), 11 7 GOLDSTEIN, HYMAN (see Frazier, Davis, GOLDSTEIN, A D
- GOLDBERG), 988 GOLINO, MARIE (see HOMER AND MCNALL), 29
- GOTTSCHALK, WILLIAM (see TRICOMI, AMOROSI, AND GOT S-CHALK), 681

, 1961

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GOT 8-

1132

GABER, EDWARD A., O'ROURKE, JAMES J., AND STURMAN, Martin, Arrhenoblastoma of the ovary, 773

GRAHAM, JOHN B. (see HRESHCHYSHYN, GRAHAM, AND HOL-LAND), 688

GRAHAM, WILLIAM (see MULLER, HEISER, AND GRAHAM), 867 GREENE, HARRY J. (see WOLFE, MACKLES, AND GREENE), 111

GREENE, JOHN W., JR., Carcinoma arising in adenomyosis associated with a feminizing mesenchymoma of the broad ligament, 272

GROVER, ESTELLE (see ISBELL AND GROVER), 784

H

HALL, ROBERT E., AND TODD, W. DUANE, The suspected ectopic pregnancy, 1220

HALPERIN, JACOB (SEE AARON, SILVERMAN, AND HALPERIN), 331

HAMILL, GEORGE C., JARMAN, JULIAN A., AND WYNNE, MOR-GAN D., Fetal effects of radioactive iodine therapy in a pregnant woman with thyroid cancer, 1018

HASTINGS, NEWLIN (see McNulty and Hastings), 1157 HAWVER, D. (see DUBOFF, BEHRMAN, AND HAWVER), 630 HAYT, DAVID B. (see MANN, McLARN, AND HAYT), 209

Heiser, William (see Muller, Heiser, and Graham), 867 Hellegers, Andre E., and Schruefer, John J. P. Nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in maternal and fetal blood, 377

(see Paystowsky, Hellegers, and Bruns), 372
 Hellman, Louis M., The research training grants program in developmental biology, 1961, 1276 (Editorial)

- (see Solish, Masterson, and Hellman), 57 HELWIG, FERDINAND C., Changing ratio of cervical to corpus carcinoma, 277

HENRY, GEORGE W., (see HUNTER, HENRY, AND JUDD), 1183

HERRERA, José A., Vulvulus after cesarean section, 415 (Correspondence)

HERRMAN, WALTER (see Buxton and HERRMAN), 584 HESSER, FRANK (see Cooperman, Rubovits, and Hesser),

385

HINDLE, WILLIAM (see Moore, Morton, Appledate, and Hindle), 1175

Hirst, Donald V., Office examination of fresh cancer cells

by interference phase microscopy, 138 HOLLAND, JAMES F. (see HRESHCHYSHYN, GRAHAM, AND HOLLAND), 688

HOLM, LOUIS W., PARKER, HAROLD R., AND GALLIGAN, SYLVIA JEAN, Adrenal insufficiency in postmature

Holstein calves, 1000 HOLZAEPFEL, JOHN H., RANNEY, BROOKS, AND NICOLAY, KENNETH S., An outline for the organization of

perinatal mortality studies, 906 HOMER, RICHARD S. AND McNall, EARL G., with the technical assistance of Oura, Midori, and Gulino, MARIE, Natural resistance to infectious diseases during pregnancy: possible relationship to serum properdin concentration, 29

HON, EDWARD H., AND WOHLGEMUTH, RICHARD, The electronic evaluation of fetal heart rate. IV. The effect of maternal exercise, 361

HORNBUCKLE, LLOYD A. (see CRAWFORD, ROBINSON, HORN-BUCKLE, AND GODFREY), 148

HORTON, CARRELL P. (see PAYTON, CRUMP, AND HORTON), 1009

Howard, William F. (see Hunter and Howard), 441

(see HUNTER, HOWARD, AND McCORMICK), 884 HESHCHYSHYN, MYROSLAW M., BOGEN, BEN, AND LOUGH-RAN, CHARLES H., What is the actual present-day management of the placenta in late abdominal preg-

GRAHAM, JOHN B., AND HOLLAND, JAMES F., Treatment of malignant trophoblastic growth in women, with special reference to amethopterin, 688

HUBER, CARL P., CARTER, JAMES E., AND VELLIOS, FRANK, Lesions of the circulatory system of the placenta,

HUNTER, CHARLES A., JR., AND HOWARD, WILLIAM F., Etiology of hypertension in toxemia of pregnancy,

AND McCormick, Charles O., Jr., Amelioration of the hypertension of toxemia by postpartum curettage, 884

HUNTER, JAMES S., JR. (see WILSON, HUNTER, AND DOCK-ERTY), 546

HUNTER, ROBERT G., HENRY, GEORGE W., AND JUDD, CHARLES S., JR., Physiologic or dysfunctional incompetence of the cervix, 1183

HUSTON, J. WILSON (see GARCIA, NELSON, BERNSTINE, HUS-TON, AND GARTENLAUB), 706

- (see Jones and Huston), 1033

- (see LEBHERZ, BOYCE, AND HUSTON), 658

HYMAN, CHESTER (see McCausland, Hyman, Winson, and TROTTER), 472

ISBELL, N. PAUL, AND GROVER, ESTELLE, The vaginal smear in office practice—the swab technique, 784

JACKSON, RICHARD L., Breech presentation in the primigravida, 653

JARMAN, JULIAN A. (see HAMILL, JARMAN, AND WYNNE), 1018

JENKINS, H. H. (see Diddle, O'Connor, and JENKINS), 166

JERNSTROM, ROGER S. (see WARREN AND JERNSTROM), 1036 JOHNSON, R. V., AND RODDICK, J. W., Incidence of adenomyosis in patients with endometrial adenocarcinoma,

JONES, WARREN J., JR., AND HUSTON, J. WILSON, Bilateral theca lutein cysts associated with an apparently normal pregnancy, 1033

Judd, Charles S., Jr. (see Hunter, Henry, and Judd), 1183

JUDD, GEORGE E., In the pursuit of excellence. President's address, 1073

KAMM, MICHAEL L. (566 PAGE, KAMM, AND CHAPPELL), 1094 KANTOR, HERMAN I., ROMAN, WILLIAM B., LEONARD, JOHN T., Leib, Luis, and Van Burkleo, Julia B., Cervical cytology in pregnancy, 729 -, AND STROTHER, W. K., German measles in pregnancy,

902

KAUFMAN, RAYMOND H., TOPEK, NATHAN H., AND WALL, JOHN A., Late irradiation changes in vaginal cytology, 859

KAY, SAUL, Carcinoma with squamous metaplasia of the ovary (so-called adenoacanthoma), 763

KINLAW, STACY (see DIDDLE AND KINLAW), 792

KINZEL, GERALD E., Enterocele, 1167

KIRBY, TAYLOR H. (see BARTER, ALPERT, KIRBY, AND TYN-DAL), 493

KISTNER, ROBERT W., Observation on the use of a nonsteroidal estrogen antagonist. I. Cystic disease of the breast, 233

KLEIN, MICHAEL, SABLE, MORRIS H., AND ZIRKIN, RICHARD M., Antepartum pulmonary embolism, 1237

KOBAK, A. J., AND SADOVE, MAX S., Combined paracervical and pudendal nerve blocks-a simple form of transvaginal regional anesthesia, 72

KOZINA, THOMAS J. (see KREMBS AND KOZINA), 1233 KREMBS, M. ALEX, AND KOZINA, THOMAS J., Antenatal pulmonary embolic disease, 1233

V

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P

- KRUPP, P. J., JR., STERNBERG, W. H., CLARK, W. H., ST. ROMAIN, M. J., JR., AND SMITH, R. C., Malignant mixed Müllerian neoplasms (mixed mesodermal tumors), 959
- KUMAR, D. (see BARNES AND KUMAR), 594
- KUNTZE, C. DONALD, Promazine as an adjunct to analgesia and sedation in labor, 403 (Re-evaluation)
- Kurland, Inving I., and Loughran, Charles H., Corticosteroids in the treatment of nonpatent Fallopian tubes, 243

L

- LADD, J. E. (see MARGULIS, LADD, FAHEY, AND WALSER), 840
- LANGMADE, CHARLES F., NOTRICA, SOLOMON, DEMETRIOU, JAMES, AND WARE, ARNOLD G., Pregnanediol excretion in threatened abortion, 1149
- Lash, Abraham F., The incompetent internal os of the cervix, 465
- LATOUR, J. P. A., Results in the management of preclinical carcinoma of the cervix, 511
- , and Pelletier, J. P., Incidence of uterine malignancy in postmenopausal bleeders, 146
- Laufer, Elizabeth U. (see Eskin, Laufer, and Pettit), 997
- LEBHERZ, T. B., BOYCE, C. R., AND HUSTON, J. W., Premature rupture of the membranes, 658
- AND FOBES, CLARK D., Management of endometriosis with nor-progesterone, 102
- Leib, Luis (see Kantor, Roman, Leonard, Leib, and Van Burkleo), 729
- Leonard, John T. (see Kantor, Roman, Leonard, Leib, and Van Burkleo), 729
- Levine, William, and Diamond, Bernard, Surgical procedures during pregnancy, 1046
- LITTLE, WILLIAM A. (see FRIEDMAN AND LITTLE), 817
- LOCK, FRANK R., GATLING, H. BEE, MAUZY, C. HAMPTON, AND WELLS, H. BRADLEY, Incidence of anomalous development following maternal rubella, 451
- LOUGHRAN, CHARLES H. (see Hreshchyshyn, Bogen, and LOUGHRAN), 302
- (see Kurland and Loughran), 243

M

- McCartney, Charles P. (see Burt and McCartney),
- McCausland, A. M., Hyman, Chester, Winsor, Travis, and Trotter, Alfred D., Jr., Venous distensibility during pregnancy, 472
- McCormick, Charles O., Jr. (see Hunter, Howard, and McCormick), 884
- McKean, Charles M. (see Goerke, McKean, Margolis, Glendening, and Page), 1132
- MACKLES, ABRAHAM, WOLFE, SAMUEL A., AND POZNER, SAMUEL N., Cellular atypia in endometrial glands (Arias-Stella reaction) as an aid in the diagnosis of ectopic pregnancy, 1209
- (see Schenck and Mackles), 782
- (see Wolfe, Mackles, and Greene), 111
- McLennan, Charles E., Treatment, 1104 (Symposium on endometrial cancer)
- McNall, Earl G. (see Homer and McNall), 29
- McNulty, James V., and Hastings, Newlin, Unusual lesions of the reproductive tract in infants and children, 1157
- MALCOLM, HENRY E., A plea from the wilderness, 821 (Pertinent comments)

- MANN, EDWARD C., McLARN, WILLIAM D., AND HAYT, DAVID B., The physiology and clinical significance of the uterine isthmus. Part I. The two-stage intrauterine balloon in the diagnosis and treatment of cervical incompetence, 209
- MARCHANT, Douglas J., Medical records, 190 (Pertinent comments)
- MARGUS, CYRIL C., AND MARGUS, STEWART L., Struma ovarii, 752
- MARGUS, STEWART L., Adenoacanthoma of the endon etrium, 259
- (see MARCUS AND MARCUS), 752
- Margolis, Alan J. (see Glendening, Margolis, and Pagi.), 591
- (see Goerke, McKean, Margolis, Glendening, AND Page), 1132
- MARGULIS, R. R., LADD, J. E., FAHEY, M. F., AND WALSER, H. C., Use of proteolytic enzymes in surgical complications, 840
- MARTIN, PURVIS L., AND SMITH, STEWARD H., Public relations in our maternity wards, 1079
- MASTERSON, J. G. (see Solish, Masterson, and Hellman), 57
- AND POMERANCE, WILLIAM, Factors influencing mortality rates in gynecologic malignancy, 140
- Mauzy, C. Hampton (see Lock, Gatling, Mauzy, and Wells), 451
- MENDLOWITZ, MILTON, ALTCHEK, ALBERT, NAFTCHI, NOSRAT, AND SPARK, RICHARD, Digital vascular reactivity to L-norepinephrine in the second trimester of pregnancy as a test for latent essential hypertension and toxemia, 643
- MENGERT, WILLIAM F., Intrauterine death at thirty-fourth week, 610 (Clinical problems)
- -, AND TACCHI, DOROTHY A., Pregnancy toxemia and sodium chloride, 601
- MICKAL, ABE, Intrauterine death at thirty-fourth week, 612
- (Clinical problems)

 MONTGOMERY, THADDEUS L., Detection and disposal of
- breast cancer in pregnancy, 926

 The microcosmos and man, 890
- Moore, J. George, Morton, Daniel G., Applegate, John W., and Hindle, William, Management of early carcinoma, 1175
- (see MORTON, MOORE, AND CHANG), 1115
 MORTON, DANIEL G., MOORE, J. GEORGE, AND CHANG,
 NORMAN, The disingle value of provingent layers for
- Norman, The clinical value of peritoneal lavage for cytologic examination, 1115

 (see Moore, Morton, Appledate, and Hindle), 1175
- MULLER, PAUL F., HEISER, WILLIAM, AND GRAHAM, WILLIAM, Repeat cesarean section, 867
- MUNNELL, EQUINN W., AND BONNEY, WALTER A., JR..

 Critical points of failure in the therapy of cancer
 of the cervix, 521

N

- Naftchi, Nosrat (see Mendlowitz, Altchek, Naftchi, and Spark), 643
- NAGLER, WILLI (see BACILE AND NAGLER), 320
- Nanzig, Reinard P. (see Aldridge, Nanzig, and Beaton). 941
- NASH, ARTHUR B., Incidence, 1100 (Symposium on endometrial cancer)
- NEDOSS, B. R. (see FARRAR AND NEDOSS), 124
- NELSON, JAMES H., JR. (see GARCIA, NELSON, BERNSTINE, HUSTON, AND GARTENLAUB), 706
- NEUMANN, H. H., AND FRICK, HENRY CLAY, II, Occusion of the Fallopian tubes with tantalum clips, 803
- Nicolay, Kenneth S. (see Holzaepfel, Ranney, and Nicolay), 906
- NOLAN, JAMES F., Introduction, 1099 (Symposium on endometrial cancer)

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AND VI-

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803

NOTRICA, SOLOMON (see LANGMADE, NOTRICA, DEMETRIOU, AND WARE), 1149
NOYES, ROBERT W., A technique for salpingoplasty, 812
NULSEN, R. O., Trial of thalidomide in insomnia asso-

ciated with the third trimester, 1245

0

O'CONNOR, K. A. (see DIDDLE, O'CONNOR, AND JENKINS),

O'ROURKE, JAMES J. (see GRABER, O'ROURKE, AND STUR-MAN), 773

OURA, MIDORI (see HOMER AND MCNALL), 29

PAGE, EMERY P., KAMM, MICHAEL L., AND CHAPPEL, CLIFF-ORD C., Usefulness of paracervical block in obstetrics, 1094

PAGE, ERNEST W. (see GLENDENING, MARGOLIS, AND PAGE),

- (see Goerke, McKean, Margolis, Glendening, and PAGE), 1132

- (see Woolever, Goldfien, and Page), 1137

PAI, DATTATRAYA N. (see TIETZE, PAI, TAYLOR, AND GAMBLE), 174

PARKER, HAROLD R. (see HOLM, PARKER, AND GALLIGAN), 1000

PARMELEE, ARTHUR H., JR., Prematurity and illegitimacy, 81 PAULSON, MORRIS J., Psychological concomitants of premenstrual tension, 733

PAYTON, ELEANOR, CRUMP, E. PERRY, AND HORTON, CARRELL P., Growth and development. X. Feeding practices with Negro infants 6 to 8 weeks old and their relationship to various maternal factors, 1009

PEDOWITZ, PAUL, POZNER, SAMUEL, AND ADLER, NATHAN H., Puerperal hematomas, 350

Pelletier, J. P. (see LATOUR AND PELLETIER), 146

PETERSON, JOHN H. (see BRANDY AND PETERSON), 1191

PETERSON, WILLIAM F., Lidocaine or dibucaine for saddle

block anesthesia—an analysis, 1249
Pettit, Mary DeWitt (see Eskin, Laufer, and Pettit), 997

Poidevin, L. O. S., The value of hysterography in the prediction of cesarean section wound defects, 67

POMERANCE, WILLIAM (see MASTERSON AND POMERANCE), 140 POTTS, C. RAY, AND ULLERY, JOHN C., Maternal and fetal effects of obstetric analgesia, 1253

POZNER, SAMUEL N. (SEE MACKLES, WOLFE, AND POZNER),

- (see Pedowitz, Pozner, and Adler), 350

PRITT, JOSEPH H., Sigmoidovaginostomy: a new method of obtaining satisfactory vaginal depth, 535

- (see Welch, Pratt, and Symmonds), 978

PRITCHARD, JACK A., Severe hypokalemia due to prolonged administration of chlorothiazide during pregnancy,

- (see Baldwin, Whalley, and Pritchard), 739

PRYSTOWSKY, HARRY, HELLEGERS, ANDRE E., AND BRUNS, PAUL, Fetal blood studies. XV. The carbon dioxide concentration gradient between the fetal and maternal blood of humans, 372

RADMAN, H. MELVIN, CAMPBELL, COLIN, AND COPLIN, ROBERT S., Anti-inflammatory drugs in obstetrics and gynecology, 344

RANNEY, BROOKS (see HOLZAEPFEL, RANNEY, AND NICOLAY), 906

RAI HAEL, SUMNER I., Monoamniotic twin pregnancy, 323

RAPPE, ADOLF (see BORGLIN AND RAPPE), 335

RICHART, RALPH, AND BENIRSCHKE, KURT, A male infant with a uterus, 1024

RINEHART, JAMES J. (see BREWER, RINEHART, AND DUNBAR), 574

RIVA, H. L., AND TEICH, JOHN C., Vaginal delivery after cesarean section, 501

ROBINSON, LEWIS S. (see CRAWFORD, ROBINSON, HORN-BUCKLE, AND GODFREY), 148

ROBINSON, S. C., Pelvic abscess, 250

RODDICK, J. W. (see JOHNSON AND RODDICK), 268

ROMAN, WILLIAM B. (see KANTOR, ROMAN, LEONARD, LEIB, AND VAN BURKLEO), 729

ROOT, BENJAMIN, EICHNER, EDUARD, AND SUNSHINE, IRVING, Blood secobarbital levels and their clinical correlation in mothers and newborn infants, 948

ROOTH, GÖSTA, SJÖSTEDT, SVEN, AND CALIGARA, FRANCO, Acid-base balance of the amniotic fluid, 4

- (see Sjöstedt, Rooth, and Caligara), 1

Ross, Robert A., ". . . There are classes of men" President's address, 417

RUBOVITS, FRANK E. (see COOPERMAN, RUBOVITS, AND HESS-ER), 385

S

SABLE, MORRIS H. (see Klein, Sable, and Zirkin), 1237

SADOVE, MAX S. (see KOBAK AND SADOVE), 72

St. Romain, M. J., Jr. (see Krupp, Sternberg, Clark, St. ROMAIN, AND SMITH), 959

SAMET, SHERWOOD, AND BOWMAN, HERBERT S., Fetomaternal ABO incompatibility: intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia in maternal circulation, 49

SCHAUPP, KARL L., JR., Genital tuberculosis in women, 1126 SCHENCK, SAMUEL B., AND MACKLES, ABRAHAM, Primary carcinoma of Fallopian tubes with positive smears,

SCHOENBUCHER, ALBERT K. (see BRANTLEY, DEL VALLE, AND Schoenbucher), 42

SCHREIBER, IRVING (see BOBROW AND SCHREIBER), 1230

SCHRUEFER, JOHN J. P. (see Hellegers and Schruefer), 377

SEITCHIK, JOSEPH, Endometriosis and hormone therapy, 183 (Pertinent comments)

Sheehan, H. L., Jaundice in pregnancy, 427

SHIPP, JAMES F. (see Byron, SHIPP, YONEMOTO, AND CHAP-MAN), 814

SILVERMAN, SIDNEY H. (see AARON, SILVERMAN, AND HAL-PERIN), 331

SJÖSTEDT, SVEN, ROOTH, GÖSTA, AND CALIGARA, FRANCO, The carbon dioxide tension of the amniotic fluid, 1

- (see Rooth, Sjöstedt, and Caligara), 4

SMITH, R. C. (see KRUPP, STERNBERG, CLARK, St. ROMAIN, AND SMITH), 959

SMITH, STEWARD H. (see MARTIN AND SMITH), 1079

Solish, G. I., Masterson, J. G., and Hellman, L. M., Pelvic arteriography in obstetrics, 57

SPARK, RICHARD (see MENDLOWITZ, ALTCHEK, NAFTCHI, AND SPARK), 643

Steer, Charles M. (see Wells and Steer), 1059

STERNBERG, W. H. (see KRUPP, STERNBERG, CLARK, St. Ro-MAIN, AND SMITH), 959

STEVENSON, CHARLES S., The combined treatment of carcinoma of the cervix with full irradiation therapy followed by radical pelvic operation, 156

STROTHER, W. K. (see KANTOR AND STROTHER), 902

STURMAN, MARTIN (See GRABER, O'ROURKE, AND STURMAN),

SUNSHINE, IRVING (see ROOT, EICHNER, AND SUNSHINE), 948 SYMMONDS, RICHARD E. (see WELCH, PRATT, AND SYM-MONDS), 978

Abe

AB

Abo

Abs

Abs

Ada

Ade

Ade

Ade

Ade

Adı

Am

Am

- TACCHI, DOROTHY A. (see MENGERT AND TACCHI), 601
- Taw, RICHARD L., Histology in relation to carcinogenesis, 1103 (Symposium on endometrial cancer)
- TAYLOR, CARL E. (see TIETZE, PAI, TAYLOR, AND GAMBLE), 174
- TAYLOR, CLIFFORD R., The effect of analgesia and anesthesia on the initial fetal respirations, 1260
- TAYLOR, E. STEWART, BRUNS, PAUL D., DUNGAN, IRMA W., AND DROSE, VERA E., Urinary estriol determinations in normal pregnancy, 625
- (see DEAN AND TAYLOR), 877
- TAYLOR, HOWARD C., Jr., The Australian and New Zealand Journal of Obstetrics and Gynaecology, 1071 (Editorial)
- The Pacific Coast Obstetrical and Gynecological Society, 1276 (Editorial)
- TAYMOR, MELVIN L., Laboratory and clinical effects of nortestosterone. II. The endometrial response, 95
- TEICH, JOHN C. (see RIVA AND TEICH), 501
- TENNY, BENJAMIN, AND DANDROW, ROBERT V., Clinical study of hypertensive disease in pregnancy, 8
- TIETZE, CHRISTOPHER, PAI, DATTATRAYA N., TAYLOR, CARL E., AND GAMBLE, CLARENCE J., A family planning service in rural Puerto Rico, 174
- TODD, W. DUANE (see HALL AND TODD), 1220
- TOPEK, NATHAN H. (see KAUPMAN, TOPEK, AND WALL), 859
- TORGHELE, JOHN R. (see ABRAMSON AND TORGHELE), 223 TORPIN, RICHARD, AND VAFAIE, IRAJ, The birth of Rustam,
- 185 (Pertinent comments)
- Traut, Herbert F., Problems in diagnosis of cancer of endometrium, 1102 (Symposium on endometrial cancer)
- TRICOMI, VINCENT, AMOROSI, LEO, AND GOTTSCHALK, WILL-IAM, A preliminary report on the use of Malmström's vacuum-extractor, 681
- TROTTER, ALFRED D., JR. (see McCausland, Hyman, Winsor, and Trotter), 472
- Tyndal, Charles M. (see Barter, Alpert, Kirby, and Tyndal), 493

U

Ullery, John C. (see Potts and Ullery), 1253

V

- VAFAIE, IRAJ (see TORPIN AND VAFAIE), 185 (Pertinent comments)
- Vellios, Frank (see Huber, Carter, and Vellios), 560 Vitsky, Meyer, Simple treatment of the incompetent cervical os, 1194

- W
- WALKER, VERN N., AND BAKER, WILLIAM S., A comparis n study of antihypertensive drug therapy and the modified Stroganoff method in the management of severe toxemia of pregnancy, 16
- Wall, John A. (see Kaufman, Topek, and Wall), 859
 Walser, H. C. (see Margulis, Ladd, Fahey, and Walser),
 RAD
- WARE, ANOLD G. (see LANGMADE, NOTRICA, DEMETRIOU, AND WARE), 1149
- WARREN, JAMES C., AND JERNSTROM, ROGER S., Diabetes it sipidus and pregnancy, 1036
- WATERS, EDWARD G., Culdoplastic technique for prevention and correction of vaginal vault prolapse and enterocele, 291
- Welch, John S., Pratt, Joseph H., and Symmones, Richard E., The Wertheim hysterectomy for squamous cell carcinoma of the uterine cervix, 978
- wells), 451 mous cell carcinoma of the uterine cervix, 9/8
 Wells), 451
- Wells, Josephine, and Steer, Charles M., Relationship of leukemia in children to abdominal irradiation of mothers during pregnancy, 1059
- Whalley, P. J. (see Baldwin, Whalley, and Pritchard), 739
- WILLIAMS, PHILIP C., Abdominal pregnancy with vaginal leakage of amniotic fluid, 318
- WILSON, ROBERT B., HUNTER, JAMES S., JR., AND DOCKERTY, MALCOLM B., Chorioadenoma destruens, 546
- Winsor, Travis (see McCausland, Hyman, Winsor, and Trotter), 472
- WIXTED, WILLIAM GLEESON (see EKVALL, WIXTED, AND DY-ER), 848
- Wohlgemuth, Richard (see Hon and Wohlgemuth), 361
 Wolfe, Samuel A., Mackles, Abraham, and Greene,
 Harry J., Endometriosis of the cervix, 111
- (see Mackles, Wolfe, and Pozner), 1209
- Woolever, C. A., Goldfien, Alan, and Page, Ernest W., Studies of the isolated perfused human placenta. II. Progesterone content of perfusates, 1137
- Woyroń, Janusz, Encephalocele attached to the placenta, 1028
- WYNNE, MORGAN D. (see HAMILL, JARMAN, AND WYNNE), 1018

Y

YONEMOTO, ROBERT H. (see Byron, Shipp, Yonemoto, and Chapman), 814

Z

ZEIT, PAUL R. (see CAHILL AND HILL), 970 ZIRKIN, RICHARD M. (see KLEIN, SABLE, AND ZIRKIN), 1237

Subject index

1961 nec.

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361

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AND

1237

Abdominal exploration (Fleming), 957

irradiation of mothers in pregnancy, leukemia in children, relationship (Wells and Steer), 1059 (Re-evaluation)

pregnancy, late, placenta in, management, present-day (Hreshchyshyn, Bogen, and Loughran), 302

with vaginal leakage of amniotic fluid (Williams), 318 ABO hemolytic disease of newborn, phenomenon in (Lewi and Clarke), 410 (Abst.)

incompatibility, fetomaternal, intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia in maternal circulation (Samet and Bowman), 49

isoimmunization (Haberman et al.), 829 (Abst.)

Abortion, threatened, pregnanediol excretion (Langmade et al.), 1149

Abscess, pelvic (Robinson), 250

Abstracts, 194, 410, 619, 825, 1068, 1286

Acid-base balance of amniotic fluid (Rooth, Sjöstedt, and Caligara), 4

Adaptive changes in immediate postnatal period (Karlberg), 829 (Abst.)

Adenoacanthoma, carcinoma with squamous metaplasia of ovary (Kay), 763

of endometrium (Marcus), 259

Adenocarcinoma, endometrial, patients with, adenomyosis in, incidence (Johnson and Roddick), 268

Adenohypophysis, delta cell of, natural history (Swanson and Ezrin), 200 (Abst.)

Adenomyosis, associated with feminizing mesenchymoma of broad ligament, carcinoma arising in (Greene), 272

incidence, in patients with endometrial adenocarcinoma (Johnson and Roddick), 268

Adolescent girl, pregnancy in (Aznar and Bennett), 934 Adrenal insufficiency in postmature Holstein calves (Holm, Parker, and Galligan), 1000

American Association of Obstetricians and Gynecologists, foundation prize, 624 (Item)

transactions of seventy-first annual meeting, 417 American Board of Obstetrics and Gynecology, 203, 416, 624, 832, 1072, 1288 (Items)

Amethopterin, intra-arterial infusions of pelvic tumors with (Cahill and Zeit), 970

treatment of malignant trophoblastic growth in women (Hreshchyshyn, Graham, and Holland), 688

Amino acid concentrations in fetal and maternal plasma (Glendening, Margolis, and Page), 591

Amniotic fluid, acid-base balance (Rooth, Sjöstedt, and Caligara), 4 carbon dioxide tension of (Sjöstedt, Rooth, and Cali-

gara), 1 vaginal leakage, abdominal pregnancy with (Williams),

318 Analgesia and anesthesia, effect, on initial fetal respira-

tions (Taylor), 1260 obstetric, maternal and fetal effects (Potts and Ullery), 1253

and sedation in labor, promazine as an adjunct to (Kuntze), 403 (Re-evaluation)

Anatomy, regional study of human structure (Gardner, Gray, and O'Rahilly), 1066 (B. rev.)

Anemia, megaloblastic, anticonvulsants in (Gatenby), 1070

Anesthesia, 1249-1265

analgesia and, effect, on initial fetal respirations (Taylor), 1260

cesarean section (Barter et al.), 493 problem, obstetrical, uterosacral block and (Aldridge, Nanzig, and Beaton), 941

saddle block, lidocaine or dibucaine for (Peterson), 1249 transvaginal regional, simple form, paracervical and pudendal nerve blocks, combined (Kobak and Sadove),

Anesthetics, spinal, long-term follow-up of patients (Vandam and Dripps), 198 (Abst.)

Anomalies, congenital, hydramnios and (Moya et al.), 828 (Abst.)

multiple, caused by extra autosome (Patau et al.), 412 (Abst.)

Anomalous development following maternal rubella, incidence (Lock et al.), 451

Antenatal pulmonary embolic disease (Krembs and Kozina),

Antepartum pulmonary embolism (Klein, Sable, and Zirkin), 1237

Antibacterial substances in placentas and serums of mothers and newborn infants (Coffin, Hook, and Muschel), 621 (Abst.)

Anticonvulsants in megaloblastic anemia (Gatenby), 1070 (Abst.)

Antigen U, red cell, isosensitization to, maternal (Afonso and de Alvarez), 45

Antihypertensive drug therapy and modified Stroganoff method in toxemia of pregnancy, comparison study (Walker and Baker), 16

Anti-inflammatory drugs in obstetrics and gynecology (Radman, Campbell, and Coplan), 344

Antimetabolite-metabolite combination cancer chemotherapy (Sullivan, Miller, and Sikes), 195 (Abst.)

Appendicitis, acute, in pregnancy (Black), 826 (Abst.) Arias-Stella reaction in ectopic pregnancy (Birch and Collins), 1198 (Mackles, Wolfe, and Pozner), 1209

Arrhenoblastoma of ovary (Graber, O'Rourke, and Sturman), 773

Arteriography, femoral, retrograde, in choriocarcinoma (Garcia et al.), 706 pelvic, in obstetrics (Solish, Masterson, and Hellman),

Atypical changes in endometrium (Arias-Stella reaction) in diagnosis of ectopic pregnancy (Mackles, Wolfe,

and Pozner), 1209 of genital epithelium in ectopic pregnancy (Birch and Collins), 1198

Australian and New Zealand Journal of Obstetrics and Gynaecology (Taylor, Barnes, and Brewer), 1071 (Editorial)

Autosome, extra, multiple congenital anomaly caused by (Patau et al.), 412 (Abst.)

January, pp. 1-208; February, pp. 209-416; March, pp. 417-624; April, pp. 625-832; May, pp. 833-1072; June, pp. 1073-1308.

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C

Balance, acid-base, of amniotic fluid (Rooth, Sjöstedt, and Caligara), 4

Balloon, intrauterine, two-stage, in diagnosis and treatment of cervical incompetence (Mann, McLarn, and Hayt), 209

Behavior, human, role of hormones in (Schon and Sutherland), 200 (Abst.)

Benign tumors of cervix (Farrar and Nedoss), 124
Bilateral theca lutein cysts associated with normal

Bilateral theca lutein cysts associated with normal pregnancy (Jones and Huston), 1033

Bilharziasis of ovary in Egypt (Shafeek), 1067 (B. rev.) Biological, medical and, research in Israel (Prywes), 1283 (B. rev.)

Biology, developmental, research training grants program, 1961 (Hellman), 1276 (Editorial)

Biopsy technique, multiple, for demonstration of uterine serosal endometriosis (Foraker), 810

Birth injuries of spinal cord (Leventhal), 829 (Abst.)
weights of infants of toxemic mothers (Beaudry and
Sutherland), 829 (Abst.)

Bleeders, postmenopausal, uterine malignancy in, incidence (Latour and Pelletier), 146

Blindness, color-, testicular feminization and (Stewart), 831 (Abst.)

Block paracervical, in obstetrics, usefulness (Page, Kamm, and Chappell), 1094

uterosacral, and obstetrical anesthesia problem (Aldridge, Nanzig, and Beaton), 941

Blood, fetal, studies (Prystowsky, Hellegers, and Bruns),

loss, menstrual, measurements (Baldwin, Whalley, and Pritchard), 739

maternal and fetal, nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in (Hellegers and Schruefer), 377

secobarbital levels, clinical correlation in mothers and newborn infants (Root, Eichner, and Sunshine), 948

Book reviews, 408, 615, 823, 1064, 1281

Books received, 618, 825, 1286

Breast cancer in pregnancy, detection and disposal (Montgomery), 926

chest, and esophagus, tumors, treatment (Pack and Ariel), 617 (B. rev.)

cystic disease (Kistner), 233

engorgement and lactation in nonnursing mothers, effect of estriol on (Borglin and Rappe), 335

in nonnursing mothers, prevention, suppression of postpartum lactation and (Barns), 339

Breech presentation in primigravida (Jackson), 653

Brenner tumor, origin and form (Arey), 743
Broad ligament, mesenchymoma, feminizing, adenomyosis
associated with, carcinoma arising in (Greene),
272

C

Calcium, strontium 90 and, secretion, in human milk (Lough, Hamada, and Comar), 621 (Abst.)

Calves, Holstein, postmature, adrenal insufficiency in (Holm, Parker, and Galligan), 1000

Cancer and allied diseases, treatment (Pack and Ariel), 617 (B. rev.)

breast, in pregnancy, detection and disposal (Montgomery), 926

cells, fresh, office examination, by interference phase microscopy (Hirst), 138

spread, relationship to chemotherapy (Moore, Sandberg, and Watne), 198 (Abst.)

of cervix 792-802 (see also Carcinoma of cervix) critical points of failure in therapy of (Munnell and Bonney), 521 Cancer of cervix-Cont'd

diagnosis of early forms (Wolstenholm and O'Connor).
1067 (B. rev.)

factors in prognosis, desquamation of malignant celliform (Graham and Graham), 196 (Abst.)

Mitra operation for (Mitra), 1281 (B. rev.) pelvic lymph nodes in treatment, parametrial radiogold as adjunct to radium therapy in (Baker). 797

sensitization response (Graham and Graham), 19 (Abst.)

Stage I, surgical treatment (Braunschweig), 196 (Abst.)

chemotherapeutic agents, effects, on human fetus (Sokal and Lessmann), 198 (Abst.)

chemotherapy, antimetabolite-metabolite combination (Sullivan, Miller, and Sikes), 195 (Abst.)

endometrial, symposium, 1099

gynecologic, 138-147 ovarian, treatment, with thio-TEPA (Shimanovsky and Wermel), 1287 (Abst.)

and pregnancy, 718-732

(Betson and Golden), 718

thyroid, pregnant women with, radioactive iodine therapy in, fetal effects (Hamill, Jarman, and Wynne), 1018

Carbon dioxide concentration gradient between fetal and and maternal blood of humans (Prystowsky, Hellegers, and Bruns), 372

tension of amniotic fluid (Sjöstedt, Rooth and Caligara),

Carcinoma arising in adenomyosis associated with feminizing mesenchymoma of broad ligament (Greene), 272

of cervix, 148-173 (see also Cancer of cervix) and corpus carcinoma, changing ratio (Helwig), 277 early, management (Moore et al.), 1175

growth and spread and adjunctive therapeutic measures (Diddle, O'Connor, and Jenkins), 166

irradiation therapy followed by radical pelvic operation for, combined treatment (Stevenson), 156 preclinical, results in management (Latour), 511

radical hysterectomy and pelvic lymphadenectomy (Diddle and Kinlaw), 792

in situ (Friedell, Hertig, and Younge), 1067 (B. rev.) squamous cell, Wertheim hysterectomy for (Welch, Pratt, and Symmonds), 978

Stage I or II, radiologic-surgical therapy, combined (Crawford et al.), 148

corpus, cervical carcinoma and, changing ratio (Helwig), 277

endometrial, granulosa-theca-cell tumor and (Frachtman), 779

of endometrium, 259-280

of Fallopian tubes, primary, with positive smears (Schenck and Mackles), 782

in situ of cervix (Friedell, Hertig, and Younge), 1067 with squamous metaplasia of ovary (adenoacanthoma) (Kay), 763

vulvar (Eichner), 1280 (Correspondence)

Cardiac arrest, hemorrhage and transfusion as major cause (LaVeen et al.), 827 (Abst.)

disease in pregnancy (Mendelson), 1282 (B. rev.)

malformation, congenital, in newborn period (Rowe and Cleary), 827 (Abst.)
heart block electrocardiograms fetal showing (Laks

heart block, electrocardiograms, fetal, showing (La lis and Longo), 827 (Abst.)

Carpal-Tunnel syndrome in pregnancy (Wilkinson), 201 (Abst.)

Cellular atypia in endometrial glands. (Arias-Stella reaction) in diagnosis of ectopic pregnancy (Mackles, Wolfe, and Pozner), 1209

distribution of fetal and adult hemoglobin (Breathrach), 620 (Abst.)

196

mec

nor

cells

adioker).

196

Sokal

(Sul-

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erapy

nne),

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wsky,

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, 272

277

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Velch.

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1067

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La lis

201

etion)

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rach).

6

Central Association of Obstetricians and Gynecologists, annual prize award, 416 (Items) meeting, 416 (Items)

transactions of twenty-eighth annual meeting, 833 Cervical cytology in pregnancy (Kantor et al.), 729 incompetence, diagnosis and treatment, two-stage intra-

uterine balloon in (Mann, McLarn, and Hayt),

Cervix, carcinoma (see Carcinoma of cervix; Cancer of cer-

endometriosis (Wolfe, Mackles, and Greene), 111

epithelium-stroma junction (Dougherty), 911 incompetence, physiologic or dysfunctional (Hunter, Henry, and Judd), 1183

incompetent, 1183-1197

internal os, complications after repair (Lash), 465 treatment, simple (Vitsky), 1194

tumors, benign, 111-137 (Farrar and Nedoss), 124

Cesarean section anesthesia (Barter et al.), 493

in Cincinnati, Ohio, 1950-1959 (Bryant), 480 in Iran, early account, birth of Rustam (Torpin and Vafaie), 185 (Pertinent comments)

morbidity from, postoperative (Dean and Taylor), 877 repeat (Muller, Heiser, and Graham), 867 vaginal delivery after (Riva and Teich), 501

volvulus after (Herrera), 415 (Correspondence) wound defects, prediction of, hysterography in, value

(Poidevin), 67 Chemical thermoregulation of full-term and premature newborn infants (Mestyan and Varga), 830 (Abst.)

Chemotherapeutic agents, cancer, effects, on human fetus (Sokal and Lessmann), 198 (Abst.)

Chemotherapy, cancer, antimetabolite-metabolite combination (Sullivan, Miller, and Sikes), 195 (Abst.)

spread of cancer cells and, relationship (Moore, Sandberg, and Watne), 198 (Abst.)

Chest, esophagus, and breast, tumors, treatment (Pack and Ariel), 617 (B. rev.)

Chickenpox, death due to, maternal (Fish), 199 (Abst.)

Child with 49 chromosomes (Fraccaro, Kaijser, and Lindsten), 1070 (Abst.)

Childbirth without pain (Vellay et al.), 1065 (B. rev.) safe, obstetric heritage (Thoms), 408 (B. rev.)

Childless couples, facts for (Hamblen), 1281 (B. rev.) Children, infants and, reproductive tract, lesions, unusual (McNulty and Hastings), 1157

Chloroform, levallorphan, and halothane, effect on initial fetal respirations (Taylor), 1260

Chlorothiazide in pregnancy, hypokalemia, severe, due to (Pritchard), 1241

Chorioadenoma destruens (Wilson, Hunter, and Dockerty), 546

Choriocarcinoma (Brewer, Rinehart, and Dunbar), 574 Chorionepithelioma and mole, 688-717

Registry, Albert Mathieu, report of 5 or more years' survival (Brewer, Rinehart, and Dunbar), 574

Chromosomal constitution, XO, male phenotype and, gonadal dysgenesis with (Bloise et al.), 1286 (Abst.)

sex in testicular feminization (Jacobs et al.), 831 (Abst.) trisomy and Sturge-Weber syndrome (Hayward and Bower), 1069 (Abst.)

Chromosome damage in man, x-ray-induced (Tough et al.), 1069 (Abst.)

Chromosomes, 49, child with (Fraccaro, Kaijser, and Lindsten), 1070 (Abst.)

Cha Foundation symposium on congenital malformations (Wolstenholme and O'Connor), 1285 (B. rev.)

Cigarette smoking and prematurity (Frazier et al.), 988 Cincinnati, Ohio, 1950-1959, cesarean section in (Bryant), Circulation, maternal, fibrinogenopenia in, hemolysis, intravascular, hemoglobinia, fetal, and, in ABO incompatibility, fetomaternal (Samet and Bowman), 40

Circulatory factors in relation to idopathic respiratory distress in newborn (Smith), 830 (Abst.)

system of placenta, lesions (Huber, Carter, and Vellios),

Classes of men (Ross), 417

Clinic, maternity center association, 1952-1958, report (Faison), 395 (Re-evaluation)

Clinical effects, laboratory and, of nortestosterone, endometrial response (Taymor), 95

problems, 606, 1266

study of hypertensive disease in pregnancy (Tenney and Dandrow), 8

Color-blindness, testicular feminization and (Stewart), 831 (Abst.)

Colposcope, use, in gynecological diagnosis (Andrews), 197 (Abst.)

Colposcopy (Bret and Coupez), 409 (B. rev.)

Commissurotomy, pregnancy and labor in women after (Vanina), 1287 (Abst.)

Complications of pregnancy, 1033-1052

medical, 29-44 in surgery, management (Artz and Hardy), 1066 (B. rev.) surgical, obstetrics and gynecology, proteolytic enzymes in,

use (Margulis et al.), 840 Congenital anomalies, hydramnios and (Moya et al.), 828 (Abst.)

multiple, caused by extra autosome (Patau et al.), 412 (Abst.)

cardiac malformation in newborn period (Rowe and Cleary), 827 (Abst.)

hypothroidism with goiter (Stanbury and Chapman), 412 (Abst.)

malformations, symposium, Ciba Foundation (Wolstenholme and O'Connor), 1285 (B. rev.) Contraception in rural Puerto Rico (Tietze et al.), 174

Convulsive disorder, familial, with unusual onset during intrauterine life (Badr El-Din), 831 (Abst.)

Cooper's ligament, urethrovaginal fixation to, for correction of stress incontinence, cystocele, and prclapse (Burch), 281

Cord, spinal, injuries, birth (Leventhal), 829 (Abst.) umbilical, prolapse, and follow-up of fetal survivors (Cushner), 666

Corpus carcinoma, cervical carcinoma and, changing ratio (Helwig), 277

Correspondence, 415, 623, 1280

Corticosteroids in treatment of nonpatent Fallopian tubes (Kurland and Loughran), 243

Culdoplastic technique for prevention and correction of vaginal vault prolapse and enterocele (Waters), 291

Curettage, postpartum, amelioration of hypertension of toxemia by (Hunter, Howard, and McCormick), 884 Cystic disease of breast (Kistner), 233

Cystocele, prolapse, and stress incontinence, correction, urethrovaginal fixation to Cooper's ligament for (Burch), 281

Cysts, theca lutein, bilateral, associated with normal pregnancy (Jones and Huston), 1033

Cytologic examination, peritoneal lavage for, clinical value (Morton, Moore, and Chang), 1115

Cytology, vaginal, irradiation changes in, late (Kaufman, Topek, and Wall), 859

D

Death, intrauterine, at thirty-fourth week (Mengert and Mickal), 610

maternal, due to disseminated varicella (Fish), 199 (Abst.) Delivery, labor and, 653-687

twin, fetal survival in (Aaron, Silverman, and Halperin), vaginal, after cesarian section (Riva and Teich), 501

- Delta cell of adenohypophysis, natural history (Swanson and Ezrin), 200 (Abst.)
- Descensus uteri, nomenclature for, conflict in (Friedman and Little), 817 (Pertinent comments)
- Destruens, chorioadenoma (Wilson, Hunter, and Dockerty), 546
- Detection and disposal of breast cancer in pregnancy (Montgomery), 926
- Development, growth and (Payton, Crump, and Horton), 1009
- Developmental biology, research training grants program, 1961 (Hellman), 1276 (Editorial) Diabetes insipidus and pregnancy (Warren and Jernstrom),
- 1036 Diabetic pregnancy, normal and, urinary estrogen excretion
- in (Hobkirk et al.), 200 (Abst.) Diagnosis of euthyroid hypometabolism (Goldberg), 1053
- (Re-evaluation) gynecological, use of colposcope (Andrews), 197 (Abst.) Dibucaine, lidocaine or, for saddle block anesthesia (Peter-
- son), 1249

 Digital vascular reactivity to L-norepinephrine in second trimester as test for latent essential hypertension and
- mester as test for latent essential hypertension and toxemia (Mendlowitz et al.), 643
- Diseases of newborn (Schaffer), 408 (B. rev.) Distensibility during pregnancy, venous (McCausland et al.),
- Distensibility during pregnancy, venous (McCausland et al.)
 472
- Double uterus, unification, surgical (Fisher), 807
- Drugs, anti-inflammatory, in obstetrics and gynecology (Radman, Campbell, and Coplan), 344
- Dysfunctional, physiologic or, incompetence of cervix (Hunter, Henry, and Judd), 1183

E

- Eclampsia, management (Burt and McCartney), 1266 (Clinical problems)
- pre-eclampsia-, serum lipids in (de Alvarez and Bratvold), 1140
- Ectopic pregnancy, 1198-1248
 - diagnosis, cellular atypia in endometrial glands as aid (Mackles, Wolfe, and Pozner), 1209
 - disturbed (Feeney), 197 (Abst.)
 - epithelium in, genital, atypical changes (Birch and Collins), 1198
- suspected (Hall and Todd), 1220
- Editorials, 1071, 1276
- Egypt, bilharziasis of ovary in (Shafeek), 1067 (B. rev.)
- Electrocardiograms, fetal, showing cardiac malformation, heart block (Larks and Longo), 827 (Abst.)
- Electrohysterography (Larks), 618 (B. rev.)
- Electrolyte levels of myometrium in pregnancy (Barnes and Kumar), 594
- Electronic evaluation of fetal heart rate (Hon and Wohlgemuth), 361
- Embolic disease, pulmonary, antenatal (Krembs and Kozina), 1233
- Embolism, pulmonary, antepartum (Klein, Sable, and Zir-
- kin), 1237 Embryology, human, textbook (Harrison), 823 (B. rev.)
- Encephalocele attached to placenta (Woyton), 1028 Endocrine ablation, urinary estrogens after (McAllister et al.), 412 (Abst.)
- therapy, 95-110, 233-249
- Endometrial adenocarcinoma, patients with, adenomyosis in, incidence (Johnson and Roddick), 268
- cancer, symposium, 1099
- carcinoma, granulosa-theca-cell tumor and (Frachtman), 779
- response to nortestosterone (Taymor), 95
- Endometriosis of cervix (Wolfe, Mackles, and Greene), 111 and hormone therapy (Seitchik), 183 (Pertinent comments)

- Endometriosis-Cont'd
- management with norprogesterone (Lebherz and Fobes
- uterine serosal, demonstration of, multiple biopsy technique for (Foraker), 810
- Endometrium, adenoacanthoma (Marcus), 259
- carcinoma, 259-280
- cellular atypia (Arias-Stella reaction) in diagnosis of ectopic pregnancy (Mackles, Wolfe, and Pozner), 1209
- Engorgement, breast, and lactation in nonnursing mother, effect of estriol on (Borglin and Rappe), 335
 - in nonnursing mothers, prevention, suppression of pospartum lactation and (Barns), 339
- Enterobius vermicularis granuloma of pelvis (Campbell and Bowman), 256
- Enterocele (Kinzel), 1167
- hernia of pouch of Douglas (Lenzi), 824 (B. rev.) prolapse, vaginal vault, and, culdoplastic technique for prevention and correction (Waters), 291
- Enzymes, proteolytic, use, in surgical complications, obstetrics and gynecology (Margulis et al.), 840
- Enzymology in midwifery (Rimbach), 1282 (B. rev.)
- Epithelium, genital, in ectopic pregnancy, atypical changes (Birch and Collins), 1198
- Epithelium-stroma junction in uterine cervix (Dougherty),
 911
- Equations, empirical, nomograms and, relating oxygen tension, percentage saturation, and pH in maternal and fetal blood (Hellegers and Schruefer), 377
- Errors, surgical, and safeguards (Thorek), 618 (B. rev.) Esophagus, breast, chest, and, tumors, treatment (Pack and
- Ariel), 617 (B. rev.)
 Estriol, effect, on breast engorgement and lactation in non
 - nursing mothers (Borglin and Rappe), 335 urinary, determinations in normal pregnancy (Taylor et al.), 625
- Estrogen antagonist, nonsteroidal (Kistner), 233
 - urinary, after endocrine ablation (McAllister et al.), 412 (Abst.)
 - excretion, in normal and diabetic pregnancy (Hobkirk et al.), 200 (Abst.)
- Ethamoxytrithetol in cystic disease of breast (Kistner), 233 Euthyroid hypometabolism, diagnosis (Goldberg), 1053 (Re-
- evaluation)

 Evaluation, electronic, of fetal heart rate (Hon and Wohlge-
- muth), 361
- Excellence, pursuit (Judd), 1073
- Excretion, lysine, free, in pregnancy (Bolton, Forester, and Kerley), 413 (Abst.)
- pregnanediol, in threatened abortion (Langmade et al.), 1149
- Exercise, maternal, effect on fetal heart rate (Hon and Wohlgemuth), 361
- Exploration, abdominal (Fleming), 957
- Extrauterine pregnancy, 298-322

F

Ge

Go

Gr

- Fallopian tubes, carcinoma, primary, with positive smears (Schenck and Mackles), 782
 - nonpatent, treatment, corticosteroids in (Kurland and Loughran), 243
 - occulsion, with tantalum clips (Neumann and Frick), 803
 - schistosomiasis, Manson's (Sedlis), 254
- Familial convulsive disorder with unusual onset during intrauterine life (Badr El-Din), 831 (Abst.)
- Family planning service in rural Puerto Rico (Tietze et al.),
- Feeding practices with Negro infants 6 to 8 weeks old, relationship to maternal factors (Payton, Grump, and Horton), 1009
- Fellowship, Kennedy Memorial Travel, 203 (Item)

1961

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Frick),

ing in-

et al.),

old, re-

Crump,

377

35

Female genital tuberculosis (Schaupp), 1126

Feminization, testicular, and color-blindness (Stewart), 831 (Abst.)

chromosomal sex in (Jacobs et al.), 831 (Abst.)

Feminizing mesenchymoma of broad ligament, adenomyosis associated with, carcinoma arising in (Greene), 272 Femoral arteriography, retrograde, in choriocarcinoma (Garcia et al.), 706

Fetal and adult hemoglobin, cellular distribution (Breathrach), 620 (Abst.)

blood, maternal and, nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in (Hellegers and Schruefer), 377

studies (Prystowsky, Hellegers, and Bruns), 372

effects of radioactive iodine therapy in pregnant woman with thyroid cancer (Hamill, Jarman, and Wynne), 1018

electrocardiograms showing cardiac malformation, heart block (Larks and Longo), 827 (Abst.)

heart rate, electronic evaluation (Hon and Wohlgemuth), 361

loss, glucose tolerance curve, abnormal, and (Omers), 823 (B. rev.)

maternal and, effects of obstetric analgesia (Potts and Ullery), 1253

plasma, amino acid concentrations in (Glendening, Margolis, and Page), 591

membranes, rupture, premature, spontaneous (Ekvall, Wixted, and Dyer), 848

mortality in essential hypertension (Gate), 412 (Abst.) physiology, 361-394

respirations, initial, effect of analgesia and anesthesia on (Taylor), 1260

survival in twin delivery (Aaron, Silverman, and Halperin), 331

survivors, follow-up, after prolapse of umbilical cord (Cushner), 666

Fetomaternal ABO incompatibility, intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia in maternal circulation (Samet and Bowman), 49

Fetus, human, effects of cancer chemotherapeutic agents on (Sokal and Lessmann), 198 (Abst.)

and newborn, 988-1032

Fibrinogenopenia in maternal circulation, hemolysis, intravascular, hemoglobinemia, fetal, and, in ABO incompatibility, fetomaternal (Samet and Bowman), 49

Fluid balance in obstetrics (Rhodes), 1282 (B. rev.) Foundation prize of American Association of Obstetricians and Gynecologists, 624 (Item) thesis (Hunter and Howard), 441

Genital epithelium in ectopic pregnancy, atypical changes (Birch and Collins), 1198

tuberculosis, in women (Schaupp), 1126

German measles in pregnancy (Kantor and Strother), 902 Girl, adolescent, pregnancy in (Aznar and Bennett), 934 Glucose tolerance curve, abnormal, fetal loss (Omers), 823

(B. rev.) Goiter, congenital hypothyroidism with (Stanbury and Chap-

man), 412 (Abst.) Gonadal dysgenesis (Turner's syndrome) with male phenotype and XO chromosomal constitution (Bloise et al.), 1285 (Abst.)

Gonadotropins, human, induction of ovulation in human with (Buxton and Herrmann), 584

Good factor, hemolytic disease of newborn due to (Eskin, Laufer, and Pettit), 997

Grants program, research training, in developmental biology, 1961 (Hellman), 1276 (Editorial)

Gianuloma, Enterobius vermicularis, of pelvis (Campbell and Bowman), 256

Granulosa-theca-cell tumor and endometrial carcinoma (Frachtman), 779

Grass roots (observer bias) (Barnes), 821 (Pertinent comments)

(plea from wilderness) (Malcolm), 821 (Pertinent comments)

Growth and development (Payton, Crump, and Horton), 1009

Gynecologic malignancy, mortality rates, factors influencing (Masterson and Pomerance), 140

medical, and surgical, complications of pregnancy (Guttmacher and Rovinsky), 409 (B. rev.)

obstetric and, pathology (Rewell), 1064 (B. rev.) urology (Youssef), 410 (B. rev.)

Gynecology, obstetrics and, contributions of (Shirodkar), 1064 (B. rev.)

history, short (Cianfrani), 824 (B. rev.) operative, Shaw's textbook (Howkins), 1284 (B. rev.) surgical complications, obstetrics, and, proteolytic enzymes in, use (Margulis et al.), 840

textbook (Masani), 824 (B. rev.)

н

Halochromogens in human urine associated with pregnancy and ovulation (Duboff, Behrman, and Hawver),

Halothane, chloroform, levallorphan and, effect on initial fetal respirations (Taylor), 1260

Heart block, cardiac malformation and, fetal electrocardiogram showing (Larks and Longo), 827 (Abst.)

rate, fetal, electronic evaluation (Hon and Wohlgemuth),

Hematomas, puerperal (Pedowitz, Pozner, and Adler), 350 Hemiplegia, postpartum (Fisher and Rollas), 828 (Ab.t.) Hemoglobin, fetal and adult, cellular distribution (Breathrach), 620 (Abst.)

Hemoglobinemia, fetal, intravascular hemolysis, and fibrinogenopenia in maternal circulation, in fetomaternal ABO incompatibility (Samet and Bowman), 49

Hemolytic disease of newborn, ABO (Lewi and Clarke), 411 (Abst.)

due to Good factor (Eskin, Laufer, and Pettit), 997 Rh, stillbirth in, prevention (Tovey and Valaes), 1068 (Abst.)

Hemorrhage, pelvic, intractable, control, by ligation of hypogastric artery (Binder and Mitchell), 622 (Abst.)

and transfusion, major cause of cardiac arrest (LaVeen et al.), 827 (Abst.)

uterine, functional microelements in (Lapin, Ioffe-Golubchik, and Priev), 1287 (Abst.)

Hernia, inguinal, operations (Ravitch and Hitzrot), 1064 (B. rev.)

of pouch of Douglas, enterocele (Lenzi), 824 (B. rev.) History of obstetrics and gynecology, short (Cianfrani), 824 (B. rev.)

Holstein calves, postmature, adrenal insufficiency in (Holm, Parker, and Galligan), 1000

Hormone therapy, endometriosis and (Seitchik), 183 (Pertinent comments)

Hormones, role, in human behavior (Schon and Sutherland), 200 (Abst.)

Human embryology, textbook (Harrison), 823 (B. rev.) gonadotropins, induction of ovulation in human with (Buxton and Herrmann), 584

placenta, isolated perfused, organ responses (Goerke et al.), 1132

progesterone content of perfusates (Woolever, Goldfien, and Page), 1137

structure, regional study, anatomy (Gardner, Gray, and O'Rahilly), 1066 (B. rev.)

Hydatidiform mole, hysterectomy, immediate, without curettage in (Acosta-Sison), 715 six consecutive (Endres), 711

Hydramnios and congenital anomalies (Moya et al.), 828 (Abst.)

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- Hypertension, essential, fetal mortality in (Gate), 412 (Abst.)
 - postpartum, after use of vasoconstrictor and oxytocic drugs (Casady, Moore, and Bridenbaugh), 197 (Abst.)
 - and toxemia, latent, essential, digital vascular reactivity to L-norepinephrine in second trimester of pregnancy as test (Mendlowitz et al.), 643
 - in toxemia of pregnancy, etiology (Hunter and Howard),
 441
- of toxemia, amelioration, by postpartum curettage (Hunter, Howard, and McCormick), 884
- Hypertensive disease in pregnancy, clinical study (Tenney and Dandrow), 8 and toxemia, 8-28
- Hypogastric artery, ligation, control of intractable pelvic hemorrhage by (Binder and Mitchell), 622 (Abst.)
- Hypokalemia, severe, due to chlorothiazide in pregnancy (Pritchard), 1241
- Hypometabolism, euthyroid, diagnosis (Goldberg), 1053 (Re-evaluation)
- Hypothyroidism, congenital, with goiter (Stanbury and Chapman), 412 (Abst.)
- Hysterectomy, immediate, without curettage, in hydatidiform mole (Acosta-Sison), 715
- radical, and pelvic lymphadenectomy, in cervical carcinoma (Diddle and Kinlaw), 792
- Wertheim, for squamous cell carcinoma of cervix (Welch, Pratt, and Symmonds), 978
- Hysterography in prediction of cesarean section wound defects, value (Poidevin), 67

1

- Idiopathic respiratory distress in newborn, circulatory factors in (Smith), 830 (Abst.)
- Illegitimacy, prematurity and (Parmelee), 81
- Incompatibility, ABO, fetomaternal, intravascular hemolysis, fetal hemoglobinemia, and fibrinogenopenia in maternal circulation (Samet and Bowman), 49
- Incompetence, cervical, diagnosis and treatment, two-stage intrauterine balloon in (Mann, McLarn, and Hayt), 209
 - physiologic or dysfunctional (Hunter, Henry, and Judd), 1183
- Incompetent cervix, 1183-1197
 - complications after repair (Lash), 465
 - treatment, simple (Vitsky), 1194
- Incontinence, urinary, prolapse and, 281-297
- Infant, male, with uterus (Richart and Benirschke), 1024 mortality trends, changes in, recent (Moriyama), 621 (Abst.)
- Infants and children, reproductive tract, lesions, unusual (McNulty and Hastings), 1157
- Negro, 6 to 8 weeks old, feeding practices with, relationship to maternal factors (Payton, Crump, and Horton), 1009
- newborn (see Newborn infants)
- of toxemic mothers, birth weights (Beaudry and Sutherland), 829 (Abst.)
- Infections, role, in neonatal mortality (Nelson), 828 (Abst.)
 Infectious diseases in pregnancy, natural resistance, relationship to serum properdin concentration (Homer and McNall), 29
- Inguinal hernia, operations (Ravitch and Hitzrot), 1064 (B. rev.)
- Injuries, birth, of spinal cord (Leventhal), 829 (Abst.)
- Insomnia in third trimester, thalidomide in (Nulsen), 1245 Insufficiency, adrenal, in postmature Holstein calves (Holm, Parker, and Galligan), 1000
- Interference phase microscopy, office examination of fresh cancer cells by (Hirst), 138
- International Fertility Association, 203 (Item)
- Intra-arterial infusions of pelvic tumors with amethopterin (Cahill and Zeit), 970

- Intrauterine balloon, two-stage, in diagnosis and treatment of cervical incompetence (Mann, McLarn, and Hayt), 209
 - death at thirty-fourth week (Mengert and Mickal), 610 life, familial convulsive disorder with unusual onset degraing (Badr El-Din), 831 (Abst.)
- Iodine, radioactive, therapy, fetal effects, in pregnant waman with thyroid cancer (Hamill, Jarman, and Wynne), 1018
- Iran, cesarean section in, early account, birth of Rustam (Torpin and Vafaie), 185 (Pertinent comments)
- Irradiation, abdominal, of mothers in pregnancy, leukemia in children, relationship (Wells and Steer), 1659 (Re-evaluation)
 - changes in vaginal cytology, late (Kaufman, Topek, and Wall), 859
 - therapy, full, followed by radical pelvic operation, combined treatment of carcinoma of cervix (Stevenson), 156
- Iso-antibody, platelet, in maternal serum, neonatal purpura with (Garrett et al.), 411 (Abst.)
- Isoimmunization, ABO (Haberman et al.), 829 (Abst.) problems in, 45-56
- Isolated perfused human placenta, organ responses (Goerke et al.), 1132
 - progesterone content of perfusates (Woolever, Goldfien, and Page), 1137
- Isosensitization, maternal, to red cell antigen U (Afonso and de Alvarez), 45
- Israel, medical and biological research in (Prywes), 1283 (B. rev.)
- Isthmus, uterine, physiology and clinical significance (Mann, McLarn, and Hayt), 209
- Items, 203, 416, 624, 832, 1072, 1288

J

- Jaundice in pregnancy (Sheehan), 427
- Journal of Obstetrics and Gynaecology, Australian and New Zealand (Taylor, Barnes, and Brewer), 1071 (Editorial)

K

Kennedy Memorial Travel Fellowship, James W., 203
(Item)

L

- Labor, analgesia and sedation in, promazine as adjunct to (Kuntze), 403 (Re-evaluation)
 - and delivery, 653-687
- pregnancy and, in women, after commissurotomy (Vanina), 1287 (Abst.)
- Laboratory and clinical effects of nortestosterone, endometrial response (Taymor), 95
- Lactation, breast engorgement and, in nonnursing mothers, effect of estriol on (Borglin and Rappe), 335
- postpartum, suppression, and prevention of breast engorgement in nonnursing mothers (Barns), 339

 Lamaze, Dr., thank you (Karmel), 1065 (B. rev.)
- Lawage, peritoneal, for cytologic examination, clinical value (Morton, Moore, and Chang), 1115
- Lesions of circulatory system of placenta (Huber, Carter, and Vellios), 560
 - of reproductive tract, unusual, in infants and children (McNulty and Hastings), 1157
- Leukemia in children, relationship to abdominal irradiation of mothers in pregnancy (Wells and Steer), 1059 (Re-evaluation)
- Levallorphan, halothane, and chloroform, effect on initial fetal respirations (Taylor), 1260
- Lidocaine or dibucaine for saddle block anesthesia (Peterson), 1249

Ligament, broad, mesenchymoma of, feminizing, adenomyosis associated with, carcinoma arising in (Greene),

Cooper's, urethrovaginal fixation to, for correction of stress incontinence, cystocele, and prolapse (Burch), 281 Lipids, serum, in pre-eclampsia-eclampsia (de Alvarez and Bratvold), 1140

Lymph nodes, pelvic, treatment, parametrial radiogold as adjunct to radium therapy in, in cancer of cervix (Baker), 797

Lymphadenectomy, pelvic, radical hysterectomy and, in cervical carcinoma (Diddle and Kinlaw), 792

Lysine, free, excretion in pregnancy (Bolton, Forester, and Kerley), 413 (Abst.)

M

Male infant with uterus (Richart and Benirschke), 1024 Malformation, cardiac, congenital, in newborn period (Rowe and Cleary), 827. (Abst.)

congenital, symposium, Ciba Foundation (Wolstenholme and O'Connor), 1285 (B. rev.)

heart block and, fetal electrocardiograms showing (Larks and Longo), 827 (Abst.)

Malignancy, gynecologic, mortality rates in, factors influencing (Masterson and Pomerance), 140

uterine, in postmenopausal bleeders, incidence (Latour and Pelletier), 146

Malignant cells, desquamation, factors in prognosis of cancer of cervix (Graham and Graham), 196 (Abst.) mixed Müllerian neoplasms (mixed mesodermal tumors)

(Krupp et al.), 959

Malmström's vacuum-extractor, preliminary report (Tricomi, Amorosi, and Gottschalk), 681

Man, microcosmos and (Montgomery), 890

Manson's schistosomiasis of Fallopian tube (Sedlis), 254 Mastectomy, radical, place of (Adair), 414 (Abst.)

Maternal circulation, fibrinogenopenia in, hemolysis, intravascular, hemoglobinemia, fetal, and, in fetomaternal ABO incompatibility (Samet and Bowman),

death due to disseminated varicella (Fish), 199 (Abst.) exercise, effect on fetal heart rate (Hon and Wohlgemuth), 361

fetal and, blood, carbon dioxide concentration gradient between (Prystowsky, Hellegers, and Bruns), 372

nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in (Hellegers and Schruefer), 377

effects of obstetric ana'gesia (Potts and Ullery), 1253 health and Mongolism (Coppen and Cowie), 825 (Abst.) isosensitization to red cell antigen U (Afonso and de Alvarez), 45 mortality study committees, contribution made by (Vant),

826 (Abst.)

physiology, 625-652 plasma, fetal and, amino acid concentrations in (Glendening, Margolis, and Page), 591

rubella, incidence of anomalous development following (Lock et al.), 451

serum, neonatal purpura with platelet iso-antibody in (Garrett et al.), 411 (Abst.)

Maternity center association clinic, 1952-1958, report (Faison), 395 (Re-evaluation)

hospital, staphylococcal infection, control (Corner, Crowther, and Eades), 826 (Abst.) wards, public relations in (Martin and Smith), 1079

Mathieu, Albert, Chorionepithelioma Registry, report of five or more years' survival (Brewer, Rinehart, and Dunbar), 574

Measles, German, in pregnancy (Kantor and Strother), 902 maternal, incidence of anomalous development following (Lock et al.), 451

Measurements of menstrual blood loss (Baldwin, Whalley, and Pritchard), 739

Medical and biological research in Israel (Prywes), 1283 (B. rev.)

complications of pregnancy, 29-44

records (Marchant), 190 (Pertinent comments)

surgical, and gynecological complications of pregnancy (Guttmacher and Rovinsky), 409 (B. rev.)

Megaloblastic anemia, anticonvulsants in (Gatenby), 1070 (Abst.)

Melanoma and pregnancy (Baron), 1042

Membranes, rupture, premature (Lebherz, Boyce, and Huston), 658

spontaneous (Breese), 1086

(Ekvall, Wixted, and Dyer), 848 Menstrual blood loss, measurements (Baldwin, Whalley, and Pritchard), 739

cycle, 733-742

weight, temperature changes, and psychosomatic symptomatology in relation to (Abramson and Torg-

Mesenchymoma, feminizing, of broad ligament, adenomyosis associated with, carcinoma arising in (Greene),

Mesodermal tumors, mixed (malignant mixed Müllerian neoplasms) (Krupp et al.), 959

Metabolite, antimetabolite-, combination cancer chemotherapy (Sullivan, Miller, and Sikes), 195 (Abst.)

Metaplasia, squamous (Marcus), 259

of ovary, carcinoma with (adenoacanthoma) (Kay), 763

Microcosmos and man (Montgomery), 890

Microelements in functional uterine hemorrhages (Lapin, Ioffe-Golubchik, and Priev), 1287 (Abst.)

Microscopy, interference phase, office examination of fresh cancer cells by (Hirst), 138

Midwifery, enzymology in (Rimbach), 1282 (B. rev.)

Milk, human, strontium 90 and calcium in, secretion of (Lough, Hamada, and Comar), 621 (Abst.)

Mitra operation for cancer of cervix (Mitra), 1281 (B. rev.) Mole, chorionepithelioma and, 688-717

hydatidiform, hysterectomy, immediate, without curettage in (Acosta-Sison), 715 six consecutive (Endres), 711

Mongolism, maternal health and (Coppen and Cowie), 825 (Abst.)

Monoamniotic twin pregnancy (Raphael), 323

Morbidity, postoperative, from cesarean section (Dean and Taylor), 877

Morphology of cell nucleus in sex determination (Heinz), 408 (B. rev.)

Mortality, fetal, in essential hypertension (Gate), 412 (Abst.)

maternal, study committees, contribution made by (Vant), 826 (Abst.)

neonatal infections, role in (Nelson), 828 (Abst.) perinatal, studies, organization of, outline for (Holzaepfel, Ranney, and Nicolay), 906

rates in gynecologic malignancy, factors influencing (Masterson and Pomerance), 140

trends, infant, changes in, recent (Moriyama), 621 (Abst.) Motherhood, adventure to (Offen), 617 (B. rev.)

Mothers and newborn infants, blood secobarbital levels, clinical correlation (Root, Eichner, and Sunshine), 948 placentas and serums of antibacterial substances in (Coffin, Hook, and Muschel), 621 (Abst.)

nonnursing, breast engorgement and lactation in, effect of estriol on (Borglin and Rappe), 335 prevention, suppression of postpartum lactation and

(Barns), 339 Müllerian neoplasms, malignant mixed (mixed mesodermal tumors) (Krupp et al.), 959

Myometrium, human, in pregnancy, electrolyte levels (Barnes and Kumar), 594

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, 1961

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Lustan men's) ukemia , 1059

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Goerke Gold-Afonso

, 1283 (Mann,

nd New 1 (Edi-

V., 203

junct to y (Va-

endomemothers,), 335

engorgeal value

Carter, children radiation

er), 1059 n initial

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- Negro infants 6 to 8 weeks old, feeding practices with, relationship to maternal factors (Payton, Crump, and Horton), 1009
- Neonatal mortality, infections, role in (Nelson), 828 (Abst.) period, cardiac malformation in, congenital (Rowe and Cleary), 827 (Abst.)
- purpura with platelet iso-antibody in maternal serum (Garrett et al.), 411 (Abst.)
- Neoplasms, Müllerian, malignant mixed (mixed mesodermal tumors) (Krupp et al.), 959
- Nerve blocks, paracervical and pudendal, combined, simple form of transvaginal regional anesthesia (Kobak and Sadove), 72
- New Zealand, Australian and, Journal of Obstetrics and Gynaecology (Taylor, Barnes, and Brewer), 1071 (Editorial)
- Newborn, fetus and, 988-1032
- infants, ABO hemolytic disease of, phenomenon in (Lewi and Clarke), 410 (Abst.)
 - diseases of (Shaffer), 408 (B. rev.)
 - full-term and premature, chemical thermoregulation (Mestyan and Varga), 830 (Abst.)
 - hemolytic disease, due to Good factor (Eskin, Laufer, and Pettit), 997
 - mothers and, blood secobarbital levels and clinical correlation in (Root, Eichner, and Sunshine), 948 placentas and serums of, antibacterial substances in
 - (Coffin, Hook, and Muschel), 621 (Abst.) oxygen saturation in (Cooperman, Rubovits, and Hess-
 - er), 385
 respiratory distress in, idiopathic, circulatory factors in relation to (Smith), 830 (Abst.)
 - relation to (Smith), 830 (Abst.)
 ventilatory mechanics (Sawyer, Reiman, and Wright),
 830 (Abst.)
 - vitamin K in, prophylactic use (Vietti et al.), 828
 (Abst.)
- Nomenclature for descensus uteri, conflict in (Friedman and Little), 817 (Pertinent comments)
- Nomograms and empirical equations relating oxygen tension, percentage saturation, and pH in ma.ernal and fetal blood (Hellegers and Schruefer), 377
- Nonsteroidal estrogen antagonist (Kistner), 233
- Norepinephrine, L-, digital vascular reactivity to, in second trimester, test for latent essential hypertension and toxemia (Mend.owitz et al.), 643
- Norprogesterone, endometriosis with, management (Lebherz and Fobes), 102
- Nortestosterone, laboratory and clinical effects, endometrial response (Taymor), 95

n

- Observer bias (Barnes), 821 (Pertinent comments)
- Obstetrical anesthesia problem, uterosacral block and (Aldridge, Nanzig, and Beaton), 941
- and gynecological pathology (Rewell), 1064 (B. rev.) heritage, safe childbirth (Thoms), 408 (B. rev.)
- Obstetrics (Greenhill), 616 (B. rev.)
 - fluid balance in (Rhodes), 1282 (B. rev.)
 - and gynecology, contributions of (Shirodkar), 1064 (B. rev.)
 - history, short (Cianfrani), 824 (B. rev.)
 - and surgical complications, proteolytic enzymes in, use
 (Margulis et al.), 840
- paracervical block in, usefulness (Page, Kamm, and Chappell), 1094
- Obstruction, ureteral, ureterostomy in situ for temporary control (Byron et al.), 814
- Occulsion of Fallopian tubes with tantalum clips (Neumann and Frick), 803

- Office examination of fresh cancer cells by interference phase microscopy (Hirst), 138
- practice, vaginal smear in, swab technique (Isbell and Grover), 784
- Older persons, sexual activities and attitudes (Newman and Nichols), 199 (Abst.)
- Operations for inguinal hernia (Ravitch and Hitzrot), 1064
 (B. rev.)
- Operative gynecology, Shaw's textbook (Howkins), 1284 B. rev.)
- Organization of perinatal mortality studies, outline for (Holzaepfel, Ranney, and Nicolay), 906
- Os of cervix, incompetent internal, complication after repair (Lash), 465
- Ovarian cancer, treatment, with thio-TEPA (Shimanovsky and Wermel), 1287 (Abst.)
- pregnancy, primary, unruptured (Bacile and Nagler), 320 tumors, 743-781
- Ovary, arrhenoblastoma (Graber, O'Rourke, and Sturman), 773
- bilharziasis, in Egypt (Shafeek), 1067 (B. rev.)
- squamous metaplasia of, carcinoma with (adenoacanthoma) (Kay), 763
- Ovulation in human, induction with human gonadotropins (Buxton and Herrmann), 584
- Ovum humanum (Shettles), 615 (B. rev.)
- Oxygen saturation in newborn infants (Cooperman, Rubovits, and Hesser), 385
- tension, percentage saturation, and pH in maternal and fetal blood, nomograms and empirical equations relating (Hellegers and Schruefer), 377
- Oxytocic drugs, vasoconstrictor and, postpartum hypertension after use (Casady, Moore, and Bridenbaugh), 197 (Abst.)
- Oxytocin, vasopressin and, in posterior lobe of pituitary (Currie, Adamsons, and van Dyke), 200 (Abst.)

P

- Pacific Coast Obstetrical and Gynecological Society (Barnes, Brewer, and Taylor), 1276 (Editorial)
- transactions of twenty-seventh annual meeting, 1073
- Pain, childbirth without (Vellay et al.), 1065 (B. rev.)
 Paracervical block in obstetrics, usefulness (Page, Kamm,
- and Chappell), 1094 and pudendal nerve blocks, combined, simple form of
- transvaginal regional anesthesia (Kobak and Sadove), 72

 Parametrial radiogold as adjunct to radium therapy in treat-
- Parametrial radiogold as adjunct to radium therapy in treatment of pelvic lymph nodes in cancer of cervix (Baker), 797
- Parenthood, Planned, Federation, study (poor get children) (Rainwater), 823 (B. rev.)
- Pathogenesis of experimental shock (McCluskey et al.), 825 (Abst.)
- (Abst.)
 Pathology, obstetrical and gynecological (Rewell), 1064 (B. rev.)
- Pelvic abscess (Robinson), 250
 - arteriography in obstetrics (Solish, Masterson, and Hellman), 57
- hemorrhage, intractable, control, by ligation of hypogastric artery (Binder and Mitchell), 622 (Abst.) infection, 250-258
- lymph nodes, treatment, parametrial radiogold as adjunct to radium therapy in, in cancer of cervix (Baker), 797
- lymphadenectomy, radical hysterectomy and, in certical carcinoma (Diddle and Kinlaw), 792
- operation, radical, full irradiation therapy followed by for carcinoma of cervix, combined treatment (Stevenson), 156
- tumors, intra-arterial infusions, with amethor terin (Cahill and Zeit), 970
- Pelvis, granuloma, Enterobius vermicularis (Campbell and Bowman), 256

ie, 1961

Gy. ec.

rference

ell and

nan nd

1), 1064

284 B.

or (Hol-

fter re-

anovsky

er), 320

urman),

thoma)

otropins

, Rubo-

nal and

quations

vperten-

baugh),

pituitary

(Abst.)

(Barnes.

ng, 1073

Kamm,

form of

and Sa-

in treat-

f cervix

hildren)

al.), 825

1064 (B.

nd Hell-

f hypo-

(Abst.)

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of cervix

cerrical

by, for

(St: ven-

thoy terin

bell and

Perfused isolated human placenta, organ responses (Goerke et al.), 1132

progesterone content of perfusates (Woolever, Goldfien, and Page), 1137

Pc inatal mortality studies, organization of, outline for (Holzaepfel, Ranney, and Nicolay), 906

Peritoneal lavage for cytologic examination, clinical value (Morton, Moore, and Chang), 1115

Pertinent comments, 183, 817

Phenomenon in ABO hemolytic disease of newborn (Lewi and Clarke), 410 (Abst.)

Physiologic or dysfunctional incompetence of cervix (Hunter, Henry, and Judd), 1183

Physiology, 209-232

fetal, 361-394 maternal, 625-652

of pregnancy, 1-7

Pinworm granuloma of pelvis (Campbell and Bowman), 256 Pituitary, posterior lobe, vasopressin and oxytocin in (Currie, Adamsons, and van Dyke), 200 (Abst.)

Placenta in abdominal pregnancy, late, management, present-day (Hreshchyshyn, Bogen, and Loughran), 302

encephalocele attached to (Woytoń), 1028

human, isolated perfused, organ responses (Goerke et al.), 1132

progesterone content of perfusates (Woolever, Goldfien, and Page), 1137

lesions of circulatory system of (Huber, Carter, and Vellios), 560

previa (Macafee), 201 (Abst.)

Placentas and serums of mothers and newborn infants, antibacterial substances in (Coffin, Hook, and Muschel), 621 (Abst.)

Placentation, importance, on birth weight of twins (Gedda and Poggi), 619 (Abst.)

Plasma, fetal and maternal, amino acid concentrations in (Glendening, Margolis, and Page), 591

Platelet iso-antibody in maternal serum, neonatal purpura with (Garrett et al.), 411 (Abst.)

Plea from wilderness (Malcolm), 821 (Pertinent comments)

Pneumothorax, bilateral, spontaneous, complicating pregnancy (Brantley, Del Valle, and Schoenbucher), 42 Poor get children, study by Planned Parenthood Federation

(Rainwater), 823 (Abst.)
Postmature Holstein calves, adrenal insufficiency in (Holm,

Parker, and Galligan), 1000 Postmenopausal bleeders, uterine malignancy in, incidence (Latour and Pelletier), 146

Postnatal period, immediate, adaptive changes in (Karlberg), 829 (Abst.)

Postoperative morbidity from cesarean section (Dean and Taylor), 877

Postpartum hemiplegia (Fisher and Rollas), 828 (Abst.)
hypertension after use of vasoconstrictor and oxytocic
drugs (Casady, Moore, and Bridenbaugh), 197

drugs (Casady, Moore, and Bridenbaugh), 197 (Abst.) lactation, suppression, and prevention of breast engorgement in nonnursing mothers (Barns), 339

Pouch of Douglas, hernia, or enterocele (Lenzi), 824 (B. rev.)

Preclinical carcinoma of cervix, results in management (Latour), 511

Prediction of cesarean section wound defects, hysterography in, value (Poidevin), 67

Pro-eclampsia, detection, early (Clahr, Pear, and Gabaef), 827 (Abst.)

Pre-celampsia-eclampsia, serum lipids in (de Alvarez and Bratvold), 1140

Pregnancy, abdominal, late, placenta in, management, present-day (Hreshchyshyn, Bogen, and Loughran), 302

with vaginal leakage of amniotic fluid (Williams), 318 in adolescent girl (Aznar and Bennett), 934

Pregnancy-Cont'd

appendicitis in, acute (Black), 826 (Abst.)

cancer and, 718-732

(Betson and Golden), 718

breast, detection and disposal (Montgomery), 926 cardiac disease in (Mendelson), 1282 (B. rev.)

Carpal-Tunnel syndrome in (Wilkinson), 201 (Abst.) cervical cytology in (Kantor et al.), 729

chlorothiazide in, hypokalemia, severe, due to (Pritchard),

complicated by pyocolpos (Bickers), 623 (Correspondence) complications, 1033-1052

medical, 29-44

surgical, and gynecological (Guttmacher and Rovinsky), 409 (B. rev.)

diabetes insipidus and (Warren and Jernstrom), 1036 diabetic, normal and, urinary estrogen excretion (Hobkirk et al.), 200 (Abst.)

ectopic, 1198-1248

diagnosis, cellular atypia in endometrial glands as aid (Mackles, Wolfe, and Pozner), 1209

disturbed (Feeney), 197 (Abst.)

epithelium in, genital, atypical changes (Birch and Collins), 1198

suspected (Hall and Todd), 1220

extrauterine, 298-322

hypertensive disease in, clinical study (Tenney and Dandrow), 8

infectious diseases in, natural resistance to, relationship to serum properdin concentration (Homer and McNall), 29

irradiation, abdominal, of mothers during, leukemia in children, relationship (Wells and Steer), 1059 (Re-evaluation)

jaundice in (Sheehan), 427

and labor in women after commissurotomy (Vanina), 1287

lysine excretion in, free (Bolton, Forester, and Kerley), 413 (Abst.)

measles, German, in (Kantor and Strother), 902

melanoma and (Baron), 1042

myometrium, human, in, electrolyte levels (Barnes and Kumar), 594

normal and diabetic, urinary estrogen excretion (Hobkirk et al.), 200 (Abst.)

theca lutein cysts, bilateral, associated with (Jones and Huston), 1033

urinary estriol determinations in (Taylor et al.), 625 ovarian, primary, unruptured (Bacile and Nagler), 320 and ovulation, halochromogens in human urine associated with (Duboff, Behrman, and Hawver), 630 physiology, 1-7

pneumothorax, bilateral, spontaneous, complicating (Brantley, Del Valle, and Schoenbucher), 42

second trimester, digital vascular reactivity to L-norepinephrine in, as test for latent essential hypertension and toxemia (Mendlowitz et al.), 643

sickle-cell disease in (Anderson et al.), 414 (Abst.)

surgical procedures during (Levine and Diamond), 1046 twin, monoamniotic (Raphael), 323

uteroabdominal (Clark and Bennett), 298

venous distensibility during (McCausland et al.), 472

Pregnanediol excretion in threatened abortion (Langmade et al.), 1149

Pregnant woman with thyroid cancer, radioactive iodine therapy in, fetal effects (Hamill, Jarman, and Wynne), 1018

Premature newborn infants, full-term and, chemical thermoregulation of (Mestyan and Varga), 830 (Abst.) rupture of membranes (Lebherz, Boyce, and Huston), 658

spontaneous (Breese), 1086 (Ekvall, Wixted, and Dyer), 848

Prematurity, cigarette smoking and (Frazier et al.), 988 and illegitimacy (Parmelee), 81

S

Premenstrual tension (Behrman and Buxton), 606 (Clinical problems)

psychological concomitants (Paulson), 733

Prevention of breast engorgement in nonnursing mothers, suppression of postpartum lactation and (Barns), 339

Primary carcinoma of Fallopian tubes with positive smears (Schenck and Mackles), 782

ovarian pregnancy, unruptured (Bacile and Nagler), 320 Primigravida, breech presentation in (Jackson), 653

Prolapse, stress incontinence, cystocele and, correction, urethrovaginal fixation to Gooper's ligament for (Burch), 281

of umbilical cord, and follow-up of fetal survivors (Cushner), 666

and urinary incontinence, 281-297

vaginal vault, and enterocele, culdoplastic technique for prevention and correction (Waters), 291

Promazine as adjunct to analgesia and sedation in labor (Kuntze), 403 (Re-evaluation)

Properdin concentration, serum, relationship to natural resistance to infectious diseases in pregnancy (Homer and McNall), 29

Proteolytic enzymes, use, in surgical complications, obstetrics, and gynecology (Margulis et al.), 840

Psychological concomitants of premenstrual tension (Paulson), 733

Psychosomatic symptomatology, weight, temperature changes, and, in relation to menstrual cycle (Abramson and Torghele), 223

Public relations in maternity wards (Martin and Smith), 1079

Pudendal nerve blocks, paracervical and, combined, simple form of transvaginal regional anesthesia (Kobak and Sadove), 72

Puerperal hematomas (Pedowitz, Pozner, and Adler), 350 Puerperium, 335-360

Puerto Rico, rural, family planning service (Tietze et al.), 174

Pulmonary embolic disease, antenatal (Krembs and Kozina), 1253

embolism, antepartum (Klein, Sable, and Zirkin), 1237 Purpura, neonatal, with platelet iso-antibody in maternal

serum (Garrett et al.), 411 (Abst.)
Pyocolpos, pregnancy complicated by (Bickers), 623 (Correspondence)

R

Radical mastectomy, place of (Adair), 414 (Abst.)

Radioactive iodine therapy, fetal effects, in pregnant woman with thyroid cancer (Hamill, Jarman, and Wynne), 1018

Radiogold, parametrial, as adjunct to radium therapy in treatment of pelvic lymph nodes in cancer of cervix (Baker), 797

Radiologic-surgical therapy, combined, of Stage I or II carcinoma of cervix (Crawford et al.), 148 for carcinoma of cervix (Stevenson), 156

Radium therapy, parametrial radiogold as adjunct to, in treatment of pelvic lymph nodes in cancer of cervix (Baker), 797

Recipe, president's address (Dyer), 833

Records, medical (Marchant), 190 (Pertinent comments) Re-evaluation, 395, 1053

Repeat cesarean section (Muller, Heiser, and Graham), 867 Reproductive tract, lesions, unusual, in infants and children (McNulty and Hastings), 1157

Research, medical and biological, in Israel (Prywes), 1283 (B. rev.)

training grants program in developmental biology, 1961 (Hellman), 1276 (Editorial)

Resistance, natural, to infectious diseases in pregnancy, relationship to serum properdin concentration (Homer and McNall), 29

Respirations, fetal, initial, effect of analgesia and auesthesia on (Taylor), 1260

Respiratory distress, idiopathic, in newborn, circulatory factors in relation (Smith), 830 (Abst.)

Rh hemolytic disease, stillbirth in, prevention (Tovey and Valaes), 1068 (Abst.)

Roster of American obstetrical and gynecological societies, 204

Rubella, maternal, incidence of anomalous development following (Lock et al.), 451

in pregnancy (Kantor and Strother), 902

Rupture of membranes, premature (Lebherz, Boyce, and Huston), 658

spontaneous (Breese), 1086 (Ekvall, Wixted, and Dyer), 848

Rustam, birth of, cesarean section in Iran, early account (Torpin and Vafaie), 185 (Pertinent comments)

5

Saddle block anesthesia, lidocaine or dibucaine for (Peterson), 1249

Salpingitis, clinical, etiological, and economic aspects (Ringrose), 194 (Abst.)

Salpingoplasty, technique for (Noyes), 812

Schistosomiasis, Manson's, of Fallopian tube (Sedlis), 254
Secobarbital levels, blood, clinical correlation in mothers
and newborn infants (Root, Eichner, and Sunshine), 948

Sedation, analgesia and, in labor, promazine as adjunct to (Kuntze), 403 (Re-evaluation)

Sensitization response in cancer of cervix (Graham and Graham), 195 (Abst.)

Serosal endometriosis, uterine, demonstration of, multiple biopsy technique for (Foraker), 810

Serum lipids in pre-eclampsia-eclampsia (de Alvarez and Bratvold), 1140

maternal, neonatal purpura with platelet iso-antibody in (Garrett et al.), 411 (Abst.)

properdin concentration, relationship, to natural resistance to infectious diseases in pregnancy (Homer and McNall), 29

Serums, placentas and, of mothers and newborn infants, antibacterial substances in (Coffin, Hook, and Muschel), 621 (Abst.)

Sex, chromosomal, in testicular feminization (Jacobs et al.), 831 (Abst.)

Sexual activities and attitudes in older persons (Newman and Nichols), 199 (Abst.)

Shaw's textbook of operative gynecology (Howkins), 1284
(B. rev.)

Shirodkar operations, review (Brandy and Peterson), 1191 Shock, experimental, pathogenesis (McCluskey et al.), 825 (Abst.)

Sickle-cell disease in pregnancy (Anderson et al.), 414 (Abst.)

Sigmoidovaginostomy, new method of obtaining satisfactory vaginal depth (Pratt), 535

Smear, vaginal, in office practice, swab technique (Isbell and Grover), 784

Smears, positive, carcinoma of Fallopian tubes, primary, with (Schenck and Mackles), 782

Smoking, cigarette, and prematurity (Frazier et al.), 988 Social aspects of gynecology, 174-182

of obstetrics, 81-94

Sodium chloride, toxemia of pregnancy and (Mengert and Tacchi), 601

Spinal anesthetics, long-term follow-up of patients (Vandam and Dripps), 198 (Abst.)

cord, injuries, birth (Leventhal), 829 (Abst.)

Spontaneous premature rupture of fetal membranes (Ekvall, Wixted, and Dyer), 848

ne, 1961

k Gynec,

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societies,

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aspects

is), 254

mothers

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et al.),

Newman

), 1284

), 1191

1.), 825

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isfactory

(Isbell

primary,

1.), 988

ert and

Vandam

(Ekvall,

Squamous cell carcinoma of cervix, Wertheim hysterectomy for (Welch, Pratt, and Symmonds), 978

metaplasia (Marcus), 259 of ovary, carcinoma with (adenoacanthoma) (Kay), 763 Stage I cancer of cervix, surgical treatment (Braunschweig),

196 (Abst.) or II carcinoma of cervix, radiologic-surgical therapy, combined (Crawford et al.), 148

Staphylococcal infection in maternity hospital, control (Corner, Crowther, and Eades), 826 (Abst.) Stein-Leventhal syndrome (Roberts and Haines), 194

(Abst.)

Stillbirth in Rh hemolytic disease, prevention (Tovey and Valaes), 1068 (Abst.)

Stress incontinence, cystocele, and prolapse, correction, urethrovaginal fixation to Cooper's ligament for (Burch), 281

Stroganoff method, modified, antihypertensive drug therapy and, in toxemia of pregnancy, comparison study (Walker and Baker), 16

Strontium 90 and calcium secretion, in human milk (Lough, Hamada, and Comar), 621 (Abst.)

Structure, human, regional study, anatomy (Gardner, Gray, and O'Rahilly), 1066 (B. rev.)

Struma ovarii (Marcus and Marcus), 752

Sturge-Weber syndrome, chromosomal trisomy and (Hayward and Bower), 1069 (Abst.)

Suppression of lactation, postpartum, and prevention of breast engorgement in nonnursing mothers (Barns),

Surgery, complications, management (Artz and Hardy), 1066 (B. rev.)

Surgical complications, obstetrics, and gynecology, proteolytic enzymes in, use (Margulis et al.), 840

errors and safeguards (Thorek), 618 (B. rev.) medical, and gynecological complications of pregnancy (Guttmacher and Rovinsky), 409 (B. rev.)

procedures during pregnancy (Levine and Diamond), 1046 treatment of Stage I cancer of cervix (Braunschweig), 196 (Abst.)

unification of double uterus (Fisher), 807

Survival, fetal, in twin delivery (Aaron, Silverman, and Halperin), 331

Swab technique, vaginal smear, in office practice (Isbell and Grover), 784

Symposium on congenital malformations, Ciba foundation (Wolstenholme and O'Connor), 1285 (B. rev.) on endometrial cancer, 1099

Syndrome, Carpal-Tunnel, in pregnancy (Wilkinson), 201 (Abst.)

Stein-Leventhal (Roberts and Haines), 194 (Abst.) trisomic, new (Edwards et al.), 411 (Abst.)

T

Tantalum clips, occlusion of Fallopian tubes with (Neumann and Frick), 803

Technical procedures, 57-80, 803-816

Temperature changes, weight, and psychosomatic symptomatology in relation to menstrual cycle (Abramson and Torghele), 223

Tension, carbon dioxide, of amniotic fluid (Sjöstedt, Rooth, and Caligara), 1

premenstrual (Behrman and Buxton), 606 (Clinical problems)

psychological concomitants (Paulson), 733

Testicular feminization and color-blindness (Stewart), 831 (Abst.)

chromosomal sex in (Jacobs et al.), 831 (Abst.)

Thalidomide in insomnia in third trimester (Nulsen), 1245 Theca lutein cysts, bilateral, associated with normal pregnancy (Jones and Huston), 1033

Thermoregulation, chemical, of full-term and premature newborn infants (Mestyan and Varga), 830 (Abst.)

thio-TEPA, treatment of ovarian cancer with (Shimanovsky and Wermel), 1287 (Abst.)

Thyroid cancer, pregnant woman with, radioactive iodine therapy in, fetal effects (Hamill, Jarman, and Wynne), 1018

Toxemia of pregnancy, etiology of hypertension (Hunter and Howard), 441

hypertension and, latent essential, digital vascular reactivity to L-norepinephrine in second trimester of pregnancy as test (Mendlowitz et al.), 643

amelioration, by postpartum curettage (Hunter, Howard, and McCormick), 884

hypertensive disease and, 8-28

severe, antihypertensive drug therapy and modified Stroganoff method in management (Walker and Baker), 16

sodium chloride (Mengert and Tacchi), 601

Toxemic mothers, infants of, birth weights (Beaudry and Sutherland), 829 (Abst.)

Transactions of American Association of Obstetricians and Gynecologists, seventy-first annual meeting, 417 of Central Association of Obstetricians and Gynecologists,

twenty-eighth annual meeting, 833 of Pacific Coast Obstetrical and Gynecological Society, twenty-seventh annual meeting, 1073

Transfusion, hemorrhage and, major cause of cardiac arrest (LaVeen et al.), 827 (Abst.)

Transvaginal regional anesthesia, simple form, paracervical and pudendal nerve blocks, combined (Kobak and

Trisomic syndrome, new (Edwards et al.), 411 (Abst.) Trisomy, chromosomal, and Sturge-Weber syndrome (Hayward and Bower), 1069 (Abst.)

Trophoblastic growth, malignant, in women, treatment, special reference to amethopterin (Hreshchyshyn, Graham, and Holland), 688

Tubal pregnancy, twin, unilateral (Bobrow and Schreiber),

Tuberculosis, genital, in women (Schaupp), 1126

Tumors, benign, of cervix, 111-137

(Farrar and Nedoss), 124 of breast, chest, and esophagus, treatment (Pack and Ariel), 617 (B. rev.)

Brenner, origin and form (Arey), 743

granulosa-theca-cell, and endometrial carcinoma (Frachtman), 779

mesodermal, mixed (malignant mixed Müllerian neoplasms) (Krupp et al.), 959

ovarian, 743-781

intra-arterial infusions, with amethopterin (Cahill and Zeit), 970

Turner's syndrome with male phenotype and XO chromosomal constitution (Bloise et al.), 1286 (Abst.) Twins, 323-334

birth weight, importance of placentation on (Gedda and Poggi), 619 (Abst.)

delivery, fetal survival in (Aaron, Silverman, and Halperin), 331

pregnancy, monoamniotic (Raphael), 323

tubal pregnancy, unilateral (Bobrow and Schreiber), 1230

U

Umbilical cord, prolapse, and follow-up of fetal survivors (Cushner), 666

Unilateral twin tubal pregnancy (Bobrow and Schreiber), 1230

Ureteral obstruction, temporary control, ureterostomy in situ for (Byron et al.), 814

Ureterostomy in situ for temporary control of ureteral obstruction (Byron et al.), 814

Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse (Burch), 281

- Urinary estriol determinations in normal pregnancy (Taylor et al.), 625
- estrogens after endocrine ablation (McAllister et al.), 412 (Abst.)
 - excretion in normal and diabetic pregnancy (Hobkirk et al.), 200 (Abst.)
- incontinence, prolapse and, 281-297
- Urine, human, halochromogens in, associated with pregnancy and ovulation (Duboff, Behrman, and Hawver), 630
- Urology, gynecological (Youssef), 410 (B. rev.)
- Uterine hemorrhages, functional, microelements in (Lapin, Ioffe-Golubchik, and Priev), 1287 (Abst.)
- isthmus, physiology and clinical significance (Mann, Mc-Larn, and Hayt), 209
- malignancy in postmenopausal bleeders, incidence (Latour and Pelletier), 146
- serosal endometriosis, demonstration of, multiple biopsy technique for (Foraker), 810
- wounds, non-union (Badawy), 1070 (Abst.)
- Uteroabdominal pregnancy (Clark and Bennett), 298
- Uterosacral block and obstetrical anesthesia problem (Aldridge, Nanzig, and Beaton), 941
- Uterus, double, unification, surgical (Fisher), 807 male infant with (Richart and Benirschke), 1024

V

- Vacuum-extractor, Malmström's, preliminary report (Tricomi, Amorsi, and Gottschalk), 681
- Vaginal cytology, 782-791
 - irradiation changes in, late (Kaufman, Topek, and Wall), 859
 - delivery after cesarean section (Riva and Teich), 501
 - depth, satisfactory, sigmoidovaginostomy as new method of obtaining (Pratt), 535
 - leakage of amniotic fluid, abdominal pregnancy with (Williams), 318
 - smear in office practice, swab technique (Isbell and Grover), 784
- vault prolapse and enterocele, culdoplastic technique for prevention and correction (Waters), 291

- Varicella, disseminated, maternal death due to (Fish), 199 (Abst.)
- Varicose veins, prevention and arrest by natural mea-(Cleave), 409 (B. rev.)
- Vasoconstrictor and oxytocic drugs, hypertension, postpatum, after use (Casady, Moore, and Briderbaugh), 197 (Abst.)
- Vasopressin and oxytocin in posterior lobe of pituitary (Currie, Adamsons, and van Dyke), 200 (Abst.)
- Veins, varicose, prevention and arrest by natural mean-(Cleave), 409 (B. rev.)
- Venous distensibility during pregnancy (McCausland et al.). 472
- Ventilatory mechanics in newborn (Sawyer, Reiman, and Wright), 830 (Abst.)
- Vitamin K, prophylactic use, in newborn infant (Vietti et al.), 828 (Abst.)
- Volvulus after cesarean section (Herrera), 415 (Correspondence)
- Vulvar carcinoma (Eichner), 1280 (Correspondence)

W

- Weight, temperature changes, and psychosomatic symptomatology in relation to menstrual cycle (Abramson and Torghele), 223
- Wertheim hysterectomy for squamous cell carcinoma of cervix (Welch, Pratt, and Symmonds), 978
- Wilderness, plea from (Malcolm), 821 (Pertinent comments)

X

X-ray-induced chromosome damage in man (Tough et al.), 1069 (Abst.)

V

Young girl, pregnancy in (Aznar and Bennett), 934



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The AMERICAN RED CROSS knows this, too. Through the Blood Program, licensed by the National Institutes of Health, it provides

- whole blood to hospitals served by the program
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Encourage donors to expand the availability of life's most precious fluid by giving blood wherever there are facilities for receiving it.

Capillary protective in pregnancy measures

Prenatal treatment and threatened abortion

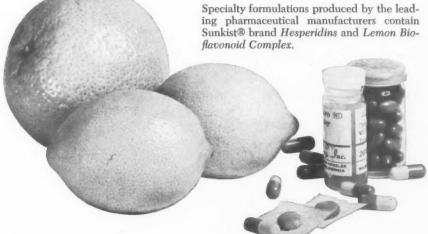
During pregnancy, fragile capillaries, increased capillary permeability, decidual bleeding, and the tendency toward edema are well recognized. Essential capillary protective factors are an integral part of the prenatal regimen.

The inclusion of Hesperidin or other citrus bioflavonoids as a "precautionary measure" in every pregnancy and as an "essential measure" in habitual aborters insures the restoration and maintenance of capillary integrity and helps prevent spontaneous abortion.

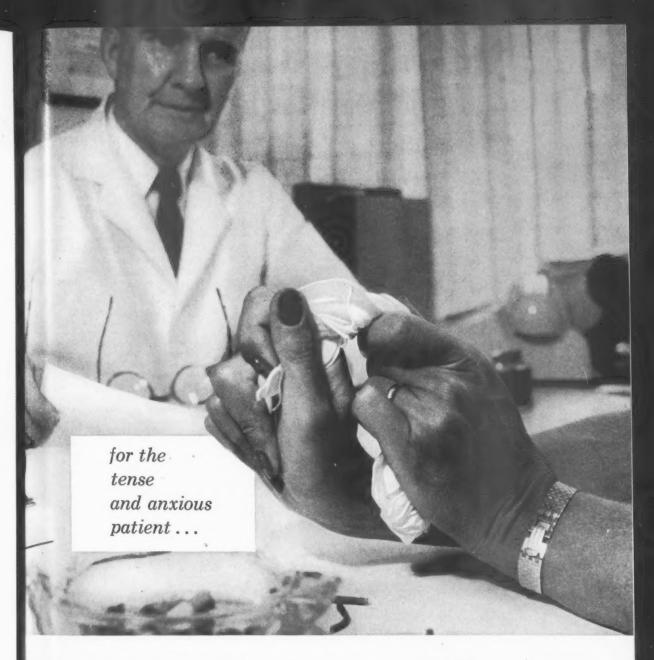
The rationale of Hespiridin and other citrus bioflavonoids - in conjunction with vitamin C, nutritional factors and other therapeutic measures - as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

Hesperidin, Lemon Bioflavonoid Complex and their naturally occurring synergist ascorbic acid are readily available capillary protective factors for the restoration and maintenance of capillary integrity and function.

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he only sustained-release tranquilizer hat does not cause autonomic side reactions

- SAFE, CONTINUOUS RELIEF of anxiety and tension for 12 hours with just one capsule—without causing autonomic side reactions and without impairing mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan²400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: Meprospan-400, each blue-topped capsule contains 400 mg. Miltown (meprobamate). Meprospan-200, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

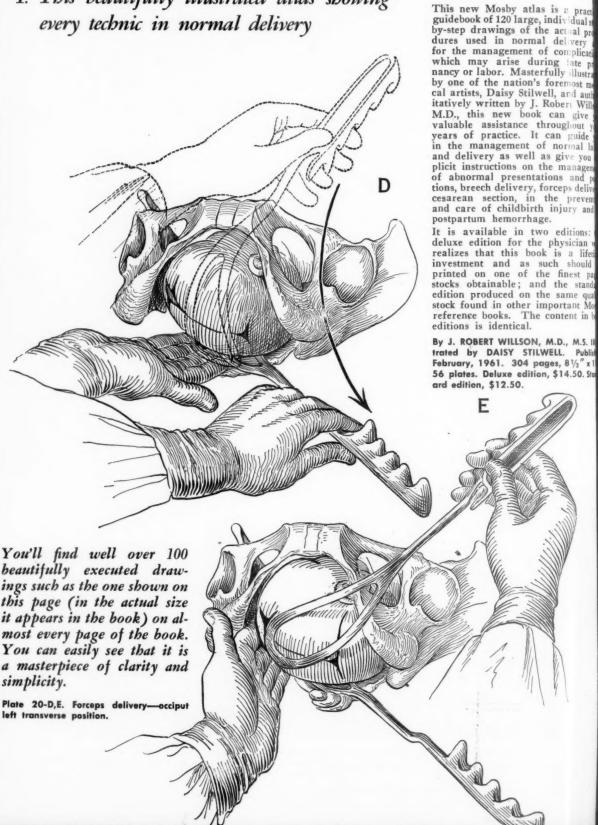


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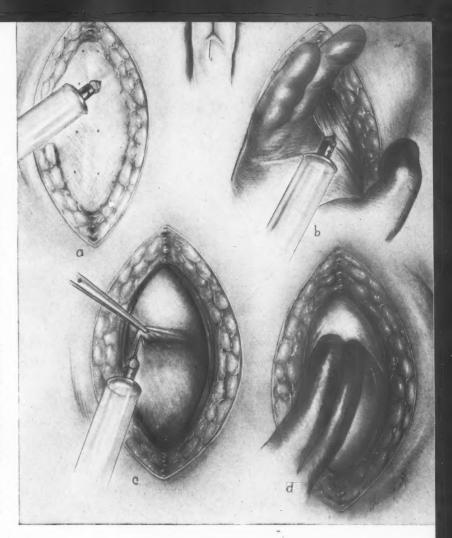
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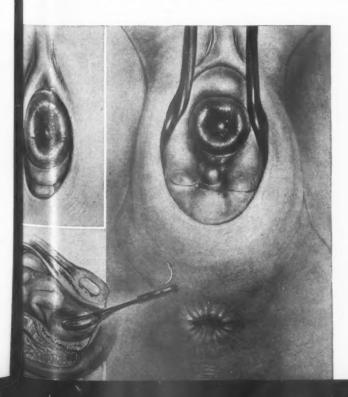
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his classic reference is an excellent applement to the ATLAS described left. This revision uses the same stemic approach to patient care at proved popular in previous edi-ins. It discusses the diagnosis and ratment of normal and abnormal regnancy and delivery and includes broughly tested procedures for the magement of complications. The uthor uses 323 illustrations to suplement the text. Much of the book as been rewritten to incorporate reent changes in diagnostic methods ad therapeutics. This edition discussthe management of habitual aboron, particularly abortions resulting om incompetence of the cervical os, e management of septic abortion editions: and new methods for the diagnosis physician want reatment of carcinoma of the is a lifeti ervix during pregnancy. Sections on the should be use of antibiotics and chemothers the standi care in omiting, essential hypertension and re-eclampsia are brought completely p to date.

A.D., M.S. III evised by J. ROBERT WILLSON, M.D., ELL. Publish A.S. Published May, 1961. 6th edition, es, 81/2" x 1 87 pages, 63/4" x 93/4", 323 illustra-\$14.50. Star ions, 1 color plate. Price \$16.50.



2 This step-by-step guide to tested procedures for normal and abnormal pregnancy and delivery and for management of complications



The detailed illustrations shown here (in the actual size they appear in the book) are just two examples of the helpful step-by-step photographs and drawings the author uses consistently throughout the book to supple-ment and elaborate upon the text matter.

Fig. 278. (Above) Local anesthesia for cesarean section. Fig. 276. (Left) Face presentation. Delivery by forceps.

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a new, rational, convenient therapy for

- Trichomonas vaginalis
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WHAT IS TRIMAGILL?

Trimagill is presented as a powder for insufflation and as dry, nongreasy vaginal inserts containing Tartaric Acid, Citric Acid, Dextrose, Boric Acid, Potassium Bitartrate, Potassium Alum, and Adhesives.

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Pathogenic micro-organisms that cause vaginal infections are incapable of surviving or propagating in a low pH environment. Trimagill produces and maintains a vaginal pH of 2.0 to 2.5—thus, infecting organisms are destroyed because an unfavorable environment is created.

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Trimagill Powder adheres to the vaginal mucosa for several hours -eliminates need for vaginal and introital packs or external pads. Trimagill Powder is easily applied during office visits; Trimagill Vaginal Inserts are recommended for patient use between office visits.

UNINTERRUPTED MEDICATION!

Trimagill treatment may safely be continued during menstruation thus preventing the normal physiological change from an acid to an alkaline pH.

TRIMAGILL IS SAFE!

No untoward reactions have been reported in over 3,000 cases treated to date. The combination of ingredients in Trimagill produces an unusually low pH with emollient properties that prevent irritation of mucous membranes.

TRIMAGILL IS PROVED BY CLINICAL EXPERIENCE!

Published papers† representing years of clinical experience in over 3,000 patients demonstrate the effectiveness and safety of Trimagill. Trimagill was used successfully in these cases primarily for acidification of the vaginal tract in treatment of vaginal infections. It was also used and is recommended as a non-absorbable agent following conization of the cervix to help eliminate postoperative sloughing, perineal odor, absorb secretion and maintain an acid pH.

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As Powder: 5 oz. Plastic Insufflator Bottles; As Vaginal Inserts: Boxes of 24. NOTE: Consult package circular for full details on instructions for use of both Powder and Vaginal Inserts.

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*Patent Applied For.

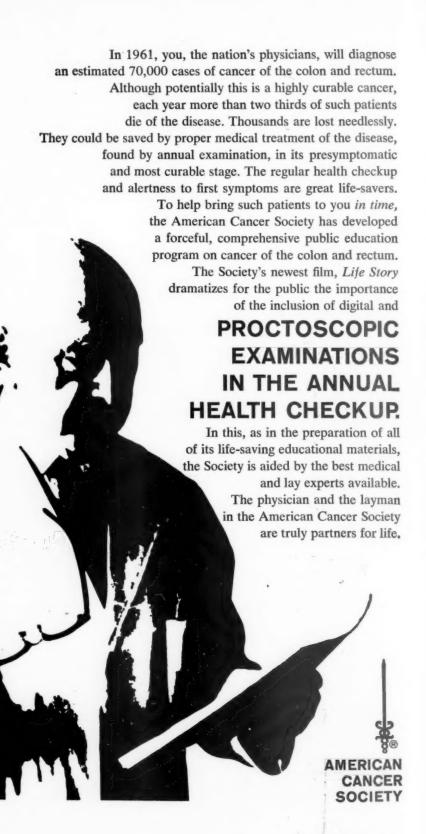
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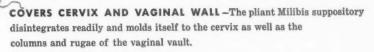
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to prevent morning sickness

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TIGAN BIBLIOGRAPHY: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, ibid. 3. J. A. Lucinian and R. H. Bohn, ibid. 4. D. W. Molander, ibid. 5. B. I. Shnider and G. L. Gold, ibid. 6. W. S. Derrick, ibid. 7. B. Wolfson and F. F. Foldes, ibid. 8. L. McLaughlin, ibid. 9. W. K. Gauthier, Discussant, ibid. 10. H. E. Davis, Discussant, ibid. 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, New York J. Med., 59:4217, 1959. 14. O. W. Doyle, Clin. Med., 7:43, 1960. 15. L. A. Nathan, Curr. Therap. Res., 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, J.A.M.A., 172:1038, 1960. 17. O. L. Davidson, J. Tennessee M.A., 53:140, 1960. 18. O. Brandman, Gastroenterology, 38:777, 1960. 19. B. A. Robin, Maryland M. J., in press. 20. A. L. Kolodny, Am. J. M. Sc., 239:682, 1960. 21. F. Cacace, Colorado GP, 2:5, 1960. 22. J. W. Bellville, I. D. J. Bross and W. S. Howland, Clin. Pharmacol. of Therap., in press. TIGAN® Hydrochloride-4-(2-dimethylaminoethoxy)-

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VISTARIL prepartum...

allays apprehension and fear without impairing ability to cooperate during labor and delivery1

reduces narcotic requirements and incidence of narcoticinduced respiratory depression: helps control nausea and vomiting; shortens stay in recovery room1,2



VISTARIL preoperatively...

allays anxiety and fear without depression of vital functions1,2

permits substantial reduction in meperidine or other narcotics with rare incidence of hypotension. respiratory depression, or other untoward effects; relaxes skeletal muscle and smooths recovery; helps control emesis1,2

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References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. P 2. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New Yo

IN BRIEF

VISTARIL Parenteral Solution is hydroxyzine hydrochloride.

Used preoperatively and postpartum, VISTARIL controls anxiety and fear, helps prevent emesis and smooths recovery. By reducing narcotic requirements substantially, VISTARIL helps to avoid narcotic-induced respiratory depression and hypotension. VISTARIL's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with VISTARIL, and it has a remarkable record of freedom from adverse reactions.

INDICATIONS: In addition to pre- and postpartum and pre- and postoperative tension and emesis, VISTARIL is clinically effective in other anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: VISTARIL dosage varies with the state and response of each patient, rather than with weight, and should therefore be individualized by the physician for optimum results. The usual dosage in prepartum and preoperative sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n. Orally, up to 400 mg. per day in divided doses.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgment of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL Parenteral Solution (hydroxyzine hydrochloride) – 10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. VISTARIL Capsules (hydroxyzine pamoate) –25, 50, and 100 mg. VISTARIL Oral Suspension (hydroxyzine pamoate) – 25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.



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Extensive evidence exists that fluorides are highly effective and extremely safe in decreasing the incidence of dental caries.

The greatest utilization of fluorine takes place during the second and third trimesters of pregnancy (2-7) and during infancy and early childhood... throughout the formation and calcification of deciduous teeth.

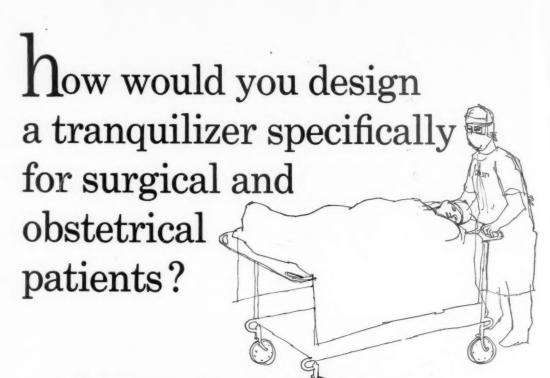
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Each pleasantly-flavored loxenge-tablet provides 1.0 mg. fluorine (as sodium fluoride) equivalent to 1.0 ppm F in drinking water. Available in bottles of 100.

One LURIDE LOZI-TAB daily ...partially dissolved in mouth before being swallowed ... affords both topical and systemic benefits of fluorine. CONTRA-INDICATED IN COMMUNITIES WITH FLUORIDATED DRINKING WATER.

REFERENCES: (1) Thoma, K. H.: Oral Pathology, ed. 4, St. Louia, 1954, The C. V. Mosby Co., pg. 371. (2) Feltman, R. and Kossel, G.: Science 122:560, 1955. (3) Gedalia, A. et al.; J. D. Res. 38:548-551, 1959. (4) Brezezinski, A. et al.: Ob. & Cyn. 15:329-321, 1960. (5) Blayney, J. R.: J. Am. Dental Assoc. 61:76-79, 1960. (6) Hall, E. W.: GP 22:111, 1960. (7) Gedalia, A. et al.: Proc. Soc. Exp. Bio. & Med. 106: 148-9, 1961.

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wouldn't you want it to:

see how closely these ATARAX advantages meet your requirements

decrease the need for narcotic pre-medication

"Hydroxyzine hydrochloride [ATARAX] appeared to have...a useful influence upon the course of narcosis. The doses of the usual drugs could be reduced by about 30%."

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The Clinical Study: A "double blind" study with 105 maternity patients, all of whom were selected because of excessive weight gain.¹

The Rx: Desoxyn Gradumet, 5, 10 or 15 mg., orally, once daily, in the morning.

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The Record: Ten women showed varying degrees of intolerance to the drug. In three, side effects were eliminated by dosage adjustment. In none of the 80 women taking Desoxyn was there any alteration in blood chemistry or EKG.

The Conclusion: "We have found Desoxyn Gradumet to be a most satisfactory drug for routine use in the management of weight control in pregnancy. We have observed no serious side effects or any exaggeration of the altered physiology of pregnancy..."

1. Chapman, J. D., Communication to Abbott Laboratories, 1961.

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(Methamphetamine Hydrochloride in Long-Release Dose Form*)

All-day appetite control from a single oral dose—5, 10 or 15 mg.



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CREAM/SUPPOSITORIES

1-5

Vaginitis (trichomonal, monilial, nonspecific), Cervicitis

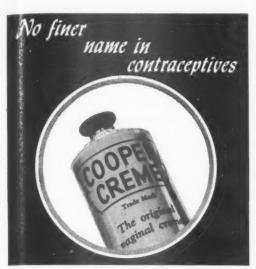
References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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Free of irritant peristaltic stimulants, ZYMENOL is safe for all your patients — geriatric to pediatric — because ZYMENOL is effective without catharsis, griping or watery stools. Contains brewers yeast to promote the growth of normal bowel flora usually deficient in constipation.

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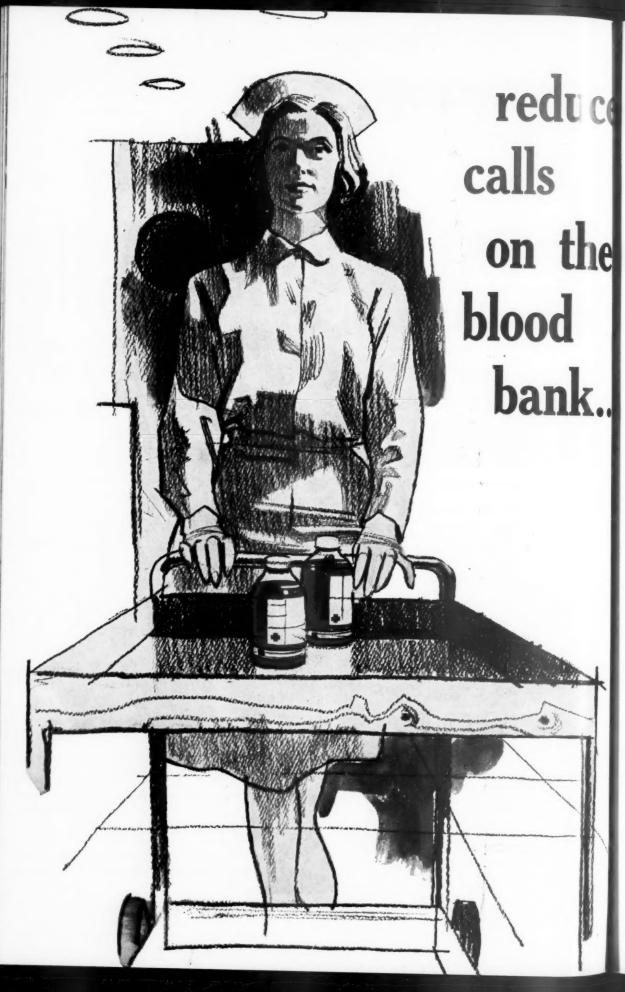
Keeps stool soft for easy passage, safely relieves distress and discomfort without danger of straining.

AFTER SURGERY: ZYMENOL helps to promote the growth of normal bowel flora in post-operative patients while assuring easy bowel movements.

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drenosem Salicylate (brand of carbazochrome salicylate)

Adrenosem helps conserve a patient's own blood. Adrenosem has become accepted pre-op medication because it minimizes the need for transfusion.

Research^{1,2} has shown that lack of capillary integrity causes abnormal bleeding four times as often as do coagulation defects. Adrenosem maintains capillary integrity by decreasing excessive capillary permeability while it also promotes retraction of severed ends.

Besides reducing need for transfusion, Adrenosem's control of bleeding results in a clearer operative field . . . makes good technic even better. Adrenosem also lessens the hazard of serious postoperative bleeding . . . reduces ooze and seepage.

Adrenosem is indicated pre- and postoperatively in surgery and also nonsurgically to control bleeding associated with vascular pathosis as in peptic ulcer, telangiectasia, purpura, ecchymosis, ulcerative colitis, and others.

There are no contraindications to Adrenosem at recommended dosage levels.

supplied: For I. M.injection only—Ampuls: 5 mg. (1 cc.) and 10 mg. (2 cc.). For oral administration—Syrup: 2.5 mg./5 cc. (1 tsp.); Tablets: 1 and 2.5 mg.

references: 1. Haden, R. L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948. 2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.

*U.S. Pat. Nos. 2581850; 2506294

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AND DOSAGE INFORMATION

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provides a comprehensive formula of essential phosphorous-free calcium plus all of the vitamins and minerals necessary to assist in the prevention and relief of ...

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DOSAGE: Four tablets daily (one tablet mid-morning, one tablet midafternoon, and two tablets at bedtime).

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Calcium Carbonate	
(Calcium	. 703.0 mg)
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Vitamin A Acetate 6000.	0 USP units
Vitamin E (as mixed Tocopherols)	5.0 I.U.
Ascorbic Acid Vitamin C)	150.0 mg
Menadione (Vitamin K)	
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Thiamine Mononitrate (Vitamin B ₁)	8.0 mg
Riboflavin (Vitamin B ₂)	8.0 mg
Niacinamide (Vitamin B ₃)	. 40.0 mg
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Ferrous Gluconate	. 320.0 mg
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Copper (as Sulfate)	. 0.60 mg
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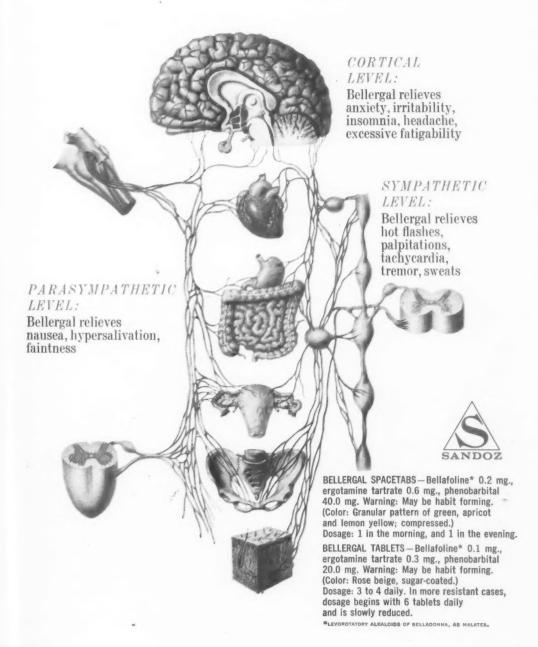
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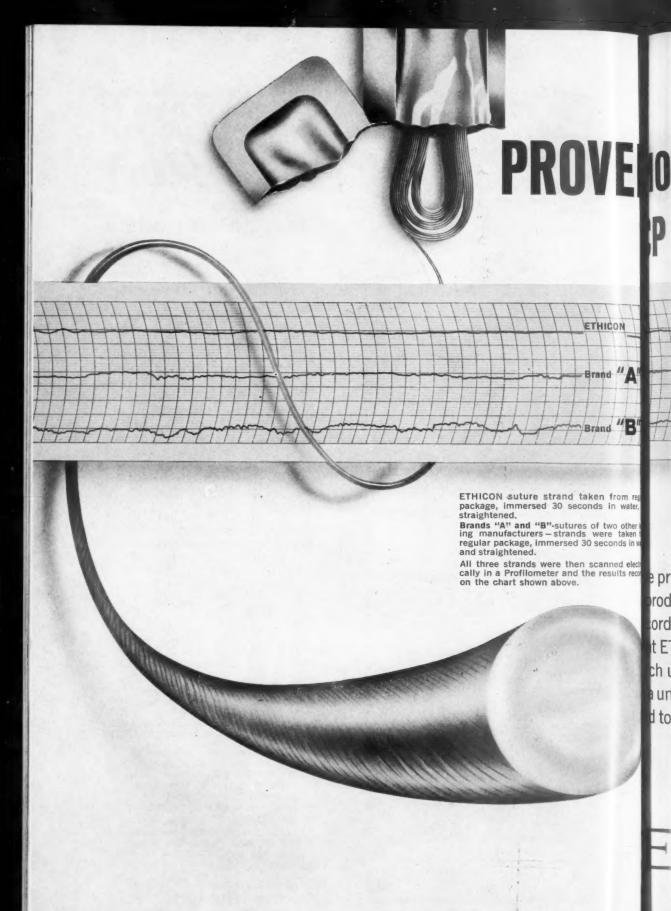
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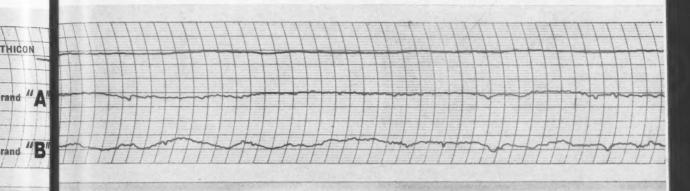
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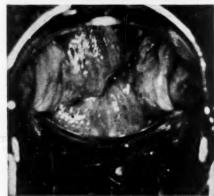
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References: 1. Lee, A. F., and Keifer, W. S.: Northwest Med. 53:1227 (Dec.) 1954. • 2. Caruso, L. J.: New York J. Med. 58:1688 (May 15) 1958. • 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268 (Sept. 22) 1956.

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INDICATIONS: Valuable in the symptomatic relief of nausea and vomiting of pregnancy. Also indicated for motion sickness, radiation sickness,

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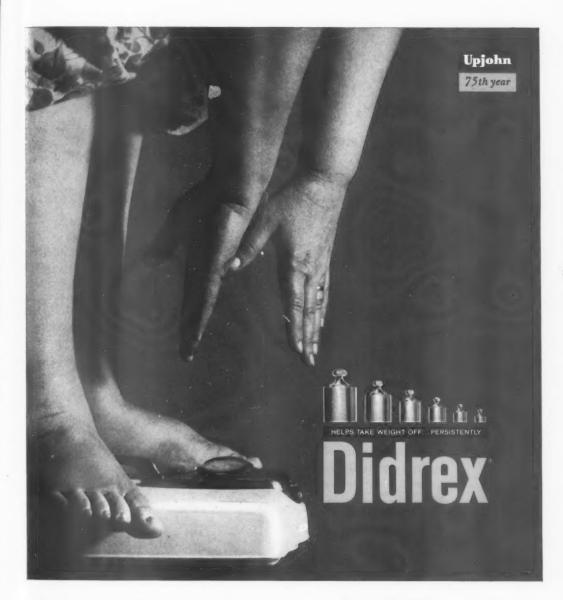
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BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N, α -dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of exogenous obesity,

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Desage: Initiate appetite control with ½ to 1 tablet (25 to 50 mg.) in mid-morning or mid-afternoon, according to the patient's eating habits for several days. Then "adjust" dosage to suit each patient's needs to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark - brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Mediar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.

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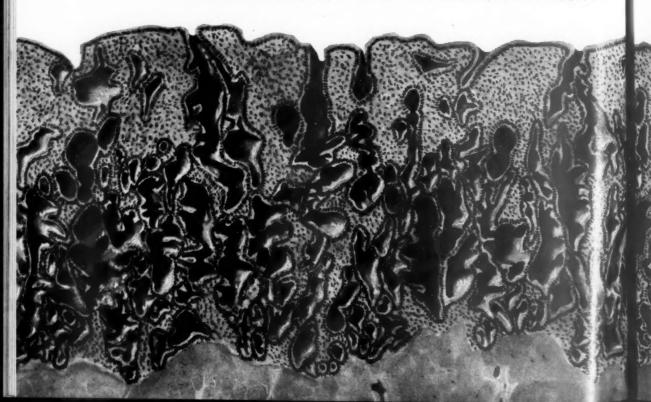
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"The use of the mixture [Deluteval 2X] offers the definite advantage of a constancy of absorption as a result of parenteral administration. Injections may be spaced at intervals of 2 weeks and the dose held constant until 'breakthrough' bleeding occurs. The tendency toward nausea in the early part of the pseudopregnancy is diminished and the difficulties of oral administration are obviated. This progestin is a caproate ester of hydroxyprogesterone and is not a so-called '19-nor-compound'. Its androgenic potential is, therefore, less than that of some other available progestins. It is not contraindicated during early pregnancy."

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 Kistner, R. W.: The use of steroidal substances in endometriosis. Clin. Pharmacol. Therap. 1:525-537 (July-Aug.) 1960.

2. Thomas, H. H.: Conservative Treatment of Endometriosis. Obstet. and Gynecol. 15:498-503 (April) 1960.



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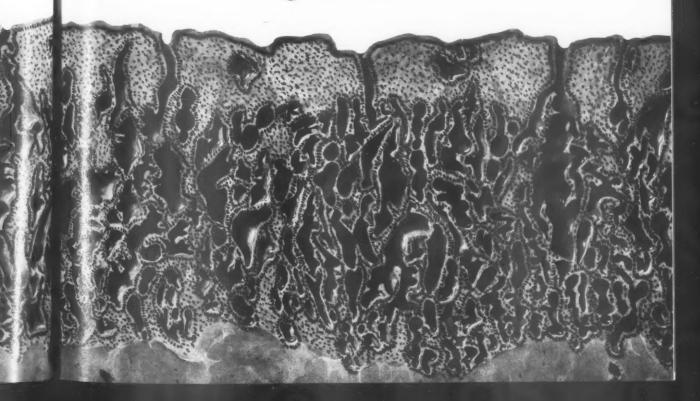
Supply: Deluteval 2X: 5 cc. vials containing 250 mg. of hydroxyprogesterone caproate and 5 mg. of estradiol valerate per cc. May be stored at room temperature. Also available—Deluteval: 2 cc. ampuls containing 125 mg. hydroxyprogesterone caproate and 2.5 mg. estradiol valerate per cc.

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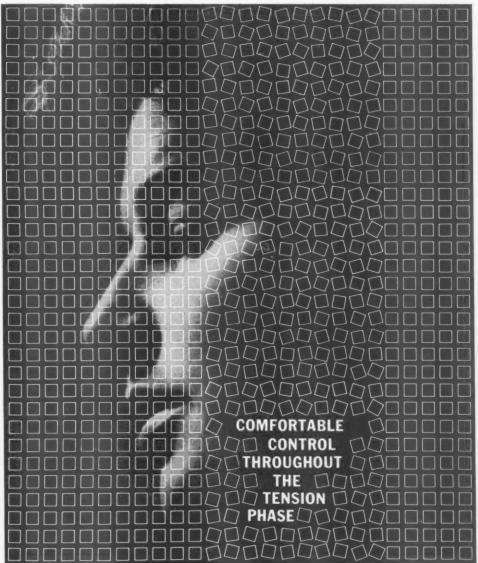
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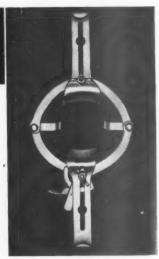
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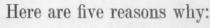
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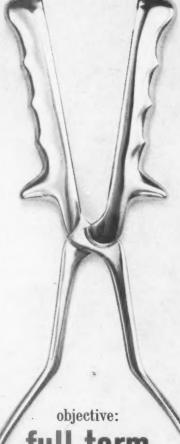
Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

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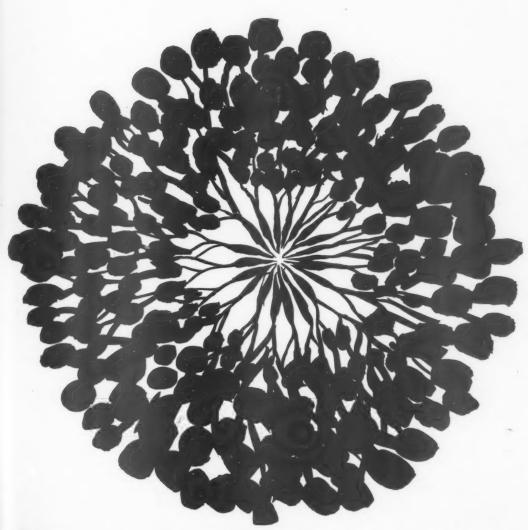
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references: (1) Antos, R. J.: Southwestern Med. 37: 236-237 (April) 1956. (2) Schoenfeld, R. C.: Am. J. Obst. & Gynec. 74:1114-1115 (Nov.) 1957.



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Each Mol-Iron Chronosule contains the equivalent of 80 mg. elemental iron. Gradual dosage release means greater patient tolerance — minimizing G.I. disorders. Marked increases in hemoglobin and hematocrit levels through sustained liberation of more absorbable Mol-Iron. All the advantages of specially processed Mol-Iron — now in the form most conducive to efficient assimilation.

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Complete information concerning the use of this drug is available on request.

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Active Ingredients: Polyoxyethylenenonylphenol 0.10%. Boric - Acid 1.0%. Phenylmercuric Acetate 0.02%, in a gum base with pH adjusted to 4.



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Nylmerate Solution has deep surface penetrating properties—Reaches innermost recesses where undesirable organisms flourish.

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Simple to use: One capful in two quarts of water. Prescribe in pint bottles.

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For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1959, p. 161.



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INDEX TO ADVERTISERS

Abdominal Supports S. H. Camp and Company 54	Ortho Pharmaceutical Corpora-	Mycostatin Vaginal Tablets E. R. Squibb & Sons 98
Adrenosem	tion 27	
The S. E. Massengill Company 92, 93	A. H. Robins Company, Inc. 112	Natabec Kapseals Parke, Davis & Company 87
Agoral Warner-Chilcott 7	Dramamine G. D. Searle & Co 71	Natalins Mead Johnson Laboratories 64, 65
Ambar Extentabs A. H. Robins Co., Inc 117	Dulcolax Geigy Pharmaceuticals 39	Norlutate Parke, Davis & Company 44, 45
Anusol Warner-Chilcott 101	Dyclone Pitman-Moore Company 22	Nylmerate Holland-Rantos Co., Inc 119
Astrafer I.V.	Eggs	
Astra Pharmaceutical Products, Inc 51	Poultry and Egg National Board 34	Ortho-Gynol and Ortho-Creme Ortho Pharmaceutical Corpora-
Atarax J. B. Roerig & Company 86	Mead Johnson Laboratories 66	O'Sullivan-O'Connor Retractors
AVC The National Drug Company 14, 90	Engran E. R. Squibb & Sons 100	Dittmar-penn Corporation 110
The Ivanonas Drag Company 14, 50	Es-A-Cort Dome Chemicals Inc 122	Premarin Ayerst Laboratories 3
Bard-Parker Sterile Blades Bard-Parker Company, Inc 69	Ferro-Sequels	Pro-Duosterone
Bellergal	Lederle Laboratories 31	Roussel Corporation19 Provera
Sandoz 95 Bendectin	Fetal Heart Monitor Hemathermatrol Corporation _ 25	The Upjohn Company 111
The Wm. S. Merrell Com-	Fosfree	Pyridium Warner-Chilcott 115
pany 62, 63 Bonine	Mission Pharmacal Co 94 Furacin	Ramses Prophylactics
Pfizer Laboratories 99	Eaton Laboratories 102	Julius Schmid, Inc 16
Charles C Thomas, Publisher 26	Furacin Vaginal Suppositories Eaton Laboratories 41	Rauwiloid Riker Laboratories Third Cover
Bucladin	Gentia-Iel	Roncovite-mf
The Stuart Company 49	Westwood Pharmaceuticals 35, 36	Lloyd Brothers, Inc 46
Caroid & Bile Salts Tablets Breon Laboratories, Inc. 48	Grafax Model "S" Grafax Instrument Co 91	Salpix Ortho Pharmaceutical Corpora-
Chymoral	Hespiridin	tion 68 Selsun
Armour Pharmaceutical Com-	Sunkist Growers 73	Abbott Laboratories 17
Colace Mead Johnson Laboratories 114	Abbott Laboratories 18	The Purdue Frederick Com-
Cooper Creme	Koromex Compact	Stuartinic
Whittaker Laboratories, Inc 91 Cortisporin	Holland-Rantos Co., Inc 74	The Stuart Company 37 Stuart Prenatal
Burroughs Wellcome & Co. (U.S.A.) Inc 60	Lanesta Gel	The Stuart Company 40
CP Surgical Gut	Breon Laboratories Inc 59 Largon	Teckla Kimonos
Ethicon, Inc 96, 97 Cyclex	Wyeth Laboratories 50	Teckla 110
Merck Sharp & Dohme 24	Roche Laboratories Second Cover	Baby" Funk & Wagnalls 94
Dactil-OB	Lubraseptic Jelly Davol Rubber Company 106	Thiosulfil-A Forte
Lakeside Laboratories 21	Luride Lozi-Tabs	Ayerst Laboratories 52 Thiosulfil Forte
Darvon Compound Eli Lilly and Company 70	Hoyt Pharmaceutical Corp 85	Ayerst Laboratories 56, 57
Declomycin Lederle Laboratories 5	Malmstrom's Vacuum Extractor AGA Corporation of America 55	Tigan Roche Laboratories 82, 83
Declostatin	Mandelamine	Trib Roche Laboratories 116
Lederle Laboratories 58 Deladumone 2X	Warner-Chilcott 23 Massengill Powder	Trichotine
E. R. Squibb & Sons 113	The S. E. Massengill Company 28, 29	The Fesler Company, Inc 61 Tricofuron
E. R. Squibb & Sons 32	Mellaril	Eaton Laboratories 38
E. R. Squibb & Sons 104, 105	Sandoz 42, 43 Mephyton	Trimagill The S. E. Massengill Com-
Demerol	Merck Sharp & Dohme 120	pany 78, 79
Winthrop Laboratories Fourth Cover	Meprospan-400 Wallace Laboratories 75	Urecholine Merck Sharp & Dohme _ 108, 109
Wallace Laboratories 30	Milibis Winthrop Laboratories 81	Vallestril
Desitin Suppositories Desitin Chemical Company 47	Milprem Wallace Laboratories 15	G. D. Searle & Co 13
esoxyn Gradumet	Miltown	Varidase Lederle Laboratories 33
Abbott Laboratories 88, 89	Wallace Laboratories 67	Vistaril
Lederle Laboratories 107	Personal Products, Inc 53	Pfizer Laboratories 84, 85
The Upjohn Company 103	Mol-Iron Chronosules White Laboratories, Inc 118	Zymenol Nicholas-Glidden Laboratories_ 91

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